A SYSTEM DYNAMICS APPROACH TO THE EFFICACY OF OXIME THERAPY IN SUB LETHAL EXPOSURE TO SARIN GAS

Thesis

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Abstract

The 2010 National Security Strategy states, “The effective dissemination of a lethal agent would endanger the lives of thousands of people and have unprecedented economic, societal, and political consequences. We must continue to work at home with first responders and health officials to reduce the risk associated with high-consequence threats”. Nerve agents, such as Sarin gas, are considered high consequence threats. The threat of use of agents such as Sarin is as much a threat today as any other time in our history. However, the suggested treatment protocol is not as precise as it could be. Debate exists over the dosing and timing of atropine and oxime treatment when combating the effects caused by exposure to nerve agents. Oxime treatment has proved to be less than effective under several situations. The research presented in this paper used a physiologically based pharmacokinetic model to determine if the current treatment protocol prescribed by the Center for Disease Control (CDC) and the U.S Army is effective in treating victims suffering from acute exposure symptoms. Then the model was used to determine what treatment should be applied to victims suffering from mild exposure symptoms. The results indicate that the current treatment prescribed by the CDC and U.S. Army is effective; however treatment with oxime therapy was not effective in alleviating symptoms for someone suffering from mild exposure. By applying these results a treatment protocol was developed for someone suffering from mild exposure symptoms to Sarin gas.

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A SYSTEM DYNAMICS APPROACH TO EFFICACY OF OXIME THERAPY IN MILD EXPOSURE TO SARIN GAS

I. Introduction

According to the 2010 National Security Strategy, "The effective dissemination of a lethal agent within a population center would endanger the lives of hundreds of thousands of people and have unprecedented economic, societal, and political consequences. We must continue to work at home with first responders and health officials to reduce the risk associated with high-consequence threats" (National Security Strategy, 2014:23). The term high consequence threat in this situation deals with weapons of mass destruction (WMD), nuclear, biological and chemical. While all three are considered high consequence threats, the use of nerve agents in recent history has prompted resurgence in the understanding of exactly how horrifying these chemicals can be when used as weapons. "The Obama administration asserted Sunday for the first time that the Syrian government used the nerve gas Sarin to kill more than 1,400 people (21 August 2013) in the world's gravest chemical weapons attack in 25 years " (Washington Post, 2014).

While the use of chemical weapons by the military during combat operations is considered appalling, the use by terrorist groups on the civilian population is even worse. The most publicized chemical attack by terrorists occurred in Japan in 1994 and 1995 by religious doomsday sect Aum Shinrikyo. The sect spread Sarin gas in an open area in the

city of Matsumoto and then later in the Tokyo Subway system (Yanagisawa et al, 1995:290). While not as devastating as planned, the terrifying impacts were felt by Japan and witnessed by the entire world. Making this an effective terrorist event.

Military professionals and the medical community have not given much thought to the specter of chemical and biological warfare. The grandfathers and great grandfathers who fought in World War I are almost all deceased and the horrific image of gassed soldiers in the trenches of Europe is a distant memory. But forgetting is no longer a luxury we can afford. Nothing has changed except the increased availability of chemical and biological weapons (Smart, 1997:12). The recent events in Syria and the not so distant incident in Japan serve as a reminder of the horrific potential chemical agents' posses. Additionally, with the increased threat of asymmetric warfare and radical groups willing to stop at nothing to promote their agenda, now more than ever, we must be able to both defend against attack and manage the casualties that might result in such an attack. Nerve agents, specifically organophosphates, are a threat to both the civilian and military environment as well as an occupational hazard to workers exposed to organophosphate based pesticides. The need to educate our healthcare providers on the proper course of action to take when confronted with causalities that are a direct result of chemical attack is vital. The education will be at a minimal cost while providing extraordinary benefits, tangibly measured in the saving of human life.

The treatment of acute poisoning due to chemical warfare agents is of limited interest to the pharmaceutical industry due to the fact that incidences are rare (Szinicz et al, 2007:24). Nonetheless, the danger is real and imminent due to the availability and accessibility in creating chemical agents as a weapon employed by armies or terrorists in

an asymmetrical warfare environment. Despite intensive endeavors by the international community, culminating in the Chemical Weapons Convention that came into force in 1997, highly toxic organophosphorus nerve agents have been stockpiled by different countries and pose a potential threat to military as well as the civilian population (Worek et al, 2007:194). Although potent, most nerve agents are relatively short acting and most are quickly degraded or dispersed to non-lethal concentrations once released. This means that following an attack there is a high likelihood that emergency services will be able to rescue a large proportion of exposed victims and transport them to emergency departments. The ultimate successful recovery of patients from the hot-zone depends largely upon treatment given within the first few hours (Smart, 1997:82).

One of the reasons that chemical and biological weapons are considered so dangerous is that the medical community, both civilian and military, have rarely ever seen patients who have suffered from exposure or have conditions that are similar to exposure to these agents. Military medical personnel of the United States have not treated a chemical causality on the battlefield for nearly nine decades and they have never treated a biological causality (Smart, 1997:11). However, terrorist attacks at home and abroad have increased the interest of civilian and military health care professionals, specifically first responders, within the Federal Emergency Management Agency (FEMA) and the Public Health Service (PHS) that would be required to respond in case of an attack on our own soil.

The potential use of highly toxic organophosphate-type chemical warfare agents during military conflicts and by terrorists emphasizes the necessity for the development of effective medical countermeasures for self and buddy aid as well as for clinical

treatment. These agents are relatively simple and inexpensive to make, easy to disperse, difficult to deter, feared by the public, and have a potential lethality to kill hundreds in one attack (Smart, 1997:79). Thus nerve agents are the ideal weapon for the terrorist. By reviewing the work conducted by Holder and Seaman the goal is to test the efficacy of the treatment regimen prescribed by the U.S. Army and the Center for Disease Control (CDC). Results of these tests will provide civilian and military medical professionals with the necessary information to save lives and reduce suffering.

The three widely accepted classes of medication that are effective in the treatment of nerve agent exposure are anticholinergics, oximes and anticonvulsants (Cannard, 2006:89). The first line of defense and the most commonly used is atropine, which is an anticholinergic. Atropine works by blocking the effects of excess acetylcholine at peripheral muscarinic sites (Rebmann et al, 2009:141). However, in high concentrations, atropine may reduce and then block neuromuscular transmissions, possibly via pre- and postsynaptic mechanisms (Wali et al, 1987:587). This makes atropine a powerful ally for first responders. To cope with the respiratory problems, antidotes reactivating inhibited acetylcholinesterase (AChE) have been developed, formally described as oxime therapy. Their clinical effectiveness is still a matter of controversy because clearly assessing oxime effects is both highly complex due to the various microscopic reactions involved and there are problems in recording the distinct clinical changes. Additionally, seizures and convulsions are possible due to exposure to nerve agents and these symptoms can be treated with anticonvulsants. Diazepam is the most commonly prescribed medication for these symptoms.

Due to the lack of information on exposure to these agents controversy exists on the proper treatment, specifically treatment for nerve agents (organophosphates). Debate exists over the dosing and timing of atropine and oxime treatment when combating the effects caused by exposure to organophosphates (Karallieddee, 1999:1074). Oxime treatment has proved to be less than effective under several situations: when the bond between the organophosphate and AChE has become irreversible, when AChE is bound by organophosphates in the system faster than it is reactivated or when oxime treatment is stopped too soon (Szinicz et al, 2007:25). And, once again, due to the low incidence rate of organophosphate poisoning little research into the development of new treatment methods has been studied.

Even with the general consensus on the use of these antidotes to mitigate organophosphate exposure symptoms, several government agencies have varying dosing strategies (Cannard, 2006:89). Antidotes against chemical warfare agents are "orphan drugs" given that these poisonings are rare (Szinicz et al, 2007:24). Therefore, they are of limited interest to the pharmaceutical industry. For this reason, and recognizing the increasing threat of terrorist or asymmetrical use of chemical warfare agents, the responsibility for research into medical countermeasures against these weapons is of primary interest to armies as well as first responders.

In order to test these disparities, physiologically based pharmacokinetic (PBPK) modeling can be used. The PBPK model is cost-effective, does not require a great deal of time and eliminates the use of extensive animal testing. The model uses compartments to describe different tissue groups that have similar pharmacokinetic properties. Several researchers have applied PBPK modeling to predict levels of organophosphates in human

tissue. In 1994, Gearhart and others created the first such PBPK model for two types of organophosphates (Seaman, 2008:9). The researchers provided evidence that a PBPK model for organophosphates could be adapted for cross-species studies and across the family of organophosphorus chemicals (Gearhart et al, 1994:52).

Due to the previously mentioned research, varying treatment guidelines and questionable effectiveness of oxime treatment lead Seaman to conduct a new study in 2008. Seaman developed a model to predict the concentration of organophosphates, atropine, oxime, acetylcholine (ACh), AChE and other chemicals in human tissue over time. In 2011 Holder continued Seaman's work with the use of PBPK modeling by further refining the data in order to develop guidance for the timing and dosage strategy for the treatment of exposure to organophosphates.

The purpose of this work is to provide medical professionals, (military and civilian), with specific details that may prove vital in alleviating symptoms caused by exposure to nerve agents, expedite triage procedures and conserve the use of drugs that maybe ineffective in some scenarios. The ultimate goal is to not only reduce the mortality rate among the initial victims but also improve the survival rate for those receiving follow on care.

Research Objectives

1. Validate the PBPK model created by Seaman and then subsequently modified by Holder and Shelley against prescribed treatment methods set forth by the CDC and U.S. Army.
2. Determine if oxime therapy is effective in alleviating symptoms for an individual with mild exposure.

II. Literature Review

History of Nerve Agents

Weapons combined with chemical agents or chemical agents operating independently have been part of the evolution of warfare since prehistoric times. The use of chemicals in warfare has been reported since Greek and Roman times, but it was not until the 19th century when rapid advances in chemistry and the chemical industry ushered in the modern era of chemical warfare. With the increased knowledge of their topological effects came the increased interest from the military. This provided the perfect nexus for the first employment of weapons of mass destruction during World War I (WWI). The modern era of chemical warfare was born on 22 April 1915 in the town of Ypres, Belgium when German troops opened nearly 6000 cylinders of chlorine gas on opposing French forces (Cannard, 2006:86). The events of WW I surrounding the use of chemical agents served as the beginning of continuously growing efforts to develop more effective chemical agents for use in warfare (Szinicz, 2005:168). It was not until more advanced delivery systems were developed that the possibility for a threat to the civilian community arose. However, the 1990s witnessed the proliferation of these agents to terrorist agencies resulting in a common awareness for the necessity to include this threat in national and international emergency and risk management plans (Szinicz, 2005:173).

The discovery and development of nerve agents was ushered in during the decades following WW I. As the understanding of the powerful effects of these chemicals grew so did the development of new weapon variants. The history of nerve agents began on 23 December 1936 when Dr. Gerhard Schrader of Germany accidently

isolated ethyl N, N-dimethylphosphoramidocyanidate, while trying to develop new insecticides (Cannard, 2006:169). He immediately recognized the potential for military application and the development of nerve agents as weapons began in earnest. The nerve agents' Tabun, Sarin and Soman were developed by Germany, each more powerful than the previous.

Table 1. Nerve Agent and Lethal Dose

OP Compound	**U.S. Army Code**	**LD_{50} (µg/kg)**
VX	VX	9.15
Soman	GD	34.1
Sarin	GB	44.3
Tabun	GA	117

After World War II (WWII) Germany's chemical warfare division was exposed to the North Atlantic Treaty Organization (NATO) and these nerve agents were sequentially designated as GA (Tabun), GB (Sarin) and GD (Soman), with G for German. Controlled animal studies of these agents revealed that death could occur within 20 minutes of exposure to very miniscule doses (Somani, 2001:26). In 1952 a British laboratory discovered another nerve agent, VX (V for venomous), while looking for a replacement to the insecticide DDT. (Somani, 2001:28). Due to the lethality of VX it was never employed as insecticide and was produced solely as a nerve agent. VX was chosen as a promising substance and full scale production commenced in 1961 in the United States (U.S.). VX appears to be one of the most effective chemical warfare agents ever produced. The lethal dose for humans is estimated to be about 0.3 mg/person for

inhalational and 5 mg/person for dermal exposure. Chemical variants were also produced in the Soviet Union and in China. Sarin and VX became the standard nerve agent in the USA (Szinicz, 2005:173). The proliferation of these nerve agents continued even though they are viewed as the most toxic known chemical warfare agents.

Even though the lethality of nerve agents has been well documented they have rarely been employed in mass during military offensive operations. Even though the Germans had stock piled tens of thousands of tons of nerve agents they were never used during WW II (Cannard, 2006:87). Speculation remains, but one of the most popular arguments is that Hitler was gassed during WW I and knew full well the horrors associated with the use of these agents of destruction.

Despite the stockpiling of enough nerve agents to kill the world's population several times over by the Soviet Union, the first documented use did not occur until the end of the Iran-Iraq war when the Iraqi Military used them against Iranian forces. Iraq military used them once again in 1988 when they conducted a chemical attack on their own people in the town of Halabja, home to 45,000 Iraqi Kurds. Five thousand people were injured and 200 killed during this attack (Cannard, 2006:87). Since these agents are relatively simple and inexpensive to make, easy to disperse, and have high lethality to kill hundreds it can be assumed that they are the perfect weapon for terrorist organizations. However, it was not until June 1994 and March 1995 that they were employed by a terrorist organization on the civilian populace. A radical group named Aum Shinrikyo attempted to spread Sarin gas in an open city, but due to the high level of dispersion of the nerve agent the attack was not as successful as they had planned. Seven were killed and 144 were injured (Okumura et al, 1996:130). The group learned from this error and

chose a target not as susceptible to changing wind speed and direction, the Tokyo subway. In March 1995 the group again released Sarin, but this time the effects were more sinister resulting in 12 deaths and injuring another 5500 (Okumura et al, 1996:130). Even though the use of nerve agents has been employed only a few times the results have helped the medical communities create countermeasures that are effective.

Toxic Mechanisms of Organophosphates

The number of accidental, suicidal and homicidal fatalities due to organophosphorus (OP) compounds is estimated at having surpassed 300,000 per year worldwide (Eyer et al, 2007:108). A lack of effective treatments, including antidotes, is considered to contribute to this high mortality rate (Buckley et al., 2004:1231). The efficacy of current antidotes is largely unproved, and many other potential antidotes have been developed but are yet to be tested in humans. Meanwhile, preparation for the terrorist use of organophosphate nerve agents is leading to the stockpiling of large amounts of these unproved antidotes to treat mass poisoning (Buckley et al., 2004:1232). Thus, research to improve the therapy of OP poisoning is compulsory.

In order to understand the effects that nerve agents impose on the body it is important to first provide a brief description of the nervous system and the enzymes involved in the process. The nervous system has two major subdivisions; the peripheral (PNS) and the central (CNS). The peripheral has two subdivisions as well, the somatic and autonomic. The autonomic portion of the nervous system deals with routine involuntary functions such as digestion, posture, and breathing. The somatic division is responsible for the voluntary control of body movements via skeletal muscles. The

central nervous system is the part of the nervous system that contains the brain and the spinal cord. It integrates information it receives from, and coordinates and influences the activity of, all parts of the body (Fox, 2004:175).

Inside the nervous system information flows from one neuron to another across a synapse, consisting of a pre-synaptic ending that contains neurotransmitters, mitochondria and other organelles and a postsynaptic ending that contains receptor sites for neurotransmitters. The space between these is referred to as the synaptic cleft and it is about 10 nm wide (Fox, 2004:169). Neural transmission across synapses of motor neurons is a one way action, from the CNS to the receptor. This occurs when neurotransmitters are released from the pre-synaptic neuron, transmitted across the synaptic cleft and then received by the post synaptic cell (Fox, 2004:169), Figure 1. ACh molecules are the most common neurotransmitters in the body and the ones that are directly affected by organophosphates (Fox, 2004:175).

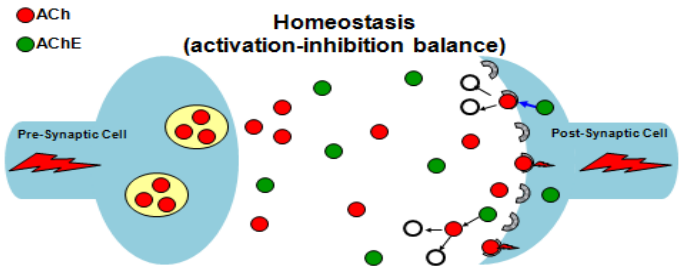


Figure 1. Synaptic Cleft at Homeostasis (Fox, 2004:169)

The pre-synaptic neurons contain small sacs that store ACh molecules. Once neural stimulation occurs, the sacs fuse with the membrane of the pre-synaptic neuron and creates a pore through which the ACh molecules diffuse into the synaptic cleft (Fox,

2004:169). Once in the cleft, ACh molecules diffuse across the synapse through interstitial fluid and briefly bind to receptor sites on the post synaptic cell (Fox, 2004:169). The bind between ACh molecules and the post synaptic receptor sites is the driving force that stimulates the neural functioning of the post synaptic cell (Fox, 2004:171). ACh molecules will dissociate from the receptor sites and maintain the potential to re-bind to the receptors for a brief period of time (Fox, 2004:171).

The human body contains two types of cholinergic receptors (having to do with acetylcholine), the muscarinic and the nicotinic. Both muscarinc and nicotinic receptors are found in the Central Nervous System and the Peripheral Nervous System. Muscarinic receptors are responsible for the stimulation of smooth muscles and the exocrine glands (sweat glands, salivary glands, and mammary glands are examples) as well as action in the central nervous system. Nicotinic receptors are located in the neuromuscular junctions of somatic muscles which are part of the peripheral nervous system associated with the voluntary control of body movements via skeletal muscles (Fox, 2004:154).

AChE are enzymes embedded on the post synaptic cell that terminate the action of the acetylcholine molecules (Fox, 2004:173). The serine hydroxyl group of the AChE binds to the acetyl portion of the ACh. When this bind occurs the choline moiety of the ACh is released and hydrolysis then separates the acetyl moiety from the AChE (Cannard, 2006:87). The choline moiety will return to the pre-synaptic cell to be recycled for the creation of new acetylcholine, while the acetyl group will react with water to form acetic acid (Cannard, 2006:87). Since AChE are the only enzymes that hydrolyze acetylcholine without their presence ACh will persist in the synaptic cleft and continually bind and disassociate with the receptor sites and cause excessive neural

stimulation (Fox, 2004:173). Overstimulation of these receptors caused by organophosphate (OP) exposure prevents the coordinated contraction of the muscles, which in turn leads to spasm and paralysis if not combated early. Symptoms associated with exposure to OPs include but are not limited to blurred vision, eye pain, headaches, increased salivation, nausea, vomiting, diarrhea, and bowel or urinary incontinence (Cannard, 2006:87).

Once in the system nerve agents work their toxic behavior by irreversibly inhibiting AChE by permanently binding to the enzyme at the esteratic site (Wright, 2009:464), Figure 2. This prevents the normal binding and rapid degradation of ACh by AChE. Normally, the action of ACh released into the synaptic cleft is terminated by the enzyme AChE via rapid cleavage of ACh into choline and acetic acid (Cannard, 2006:88). Cholinesterase, i.e. AChE and Butyrylcholinesterase (BuChE), are the main targets of OP compounds (Worek, 2005:195). The initial response is the persistence of ACh in the synaptic cleft which causes the action of ACh to be prolonged at the receptors. This produces the primary effects of nerve agents.

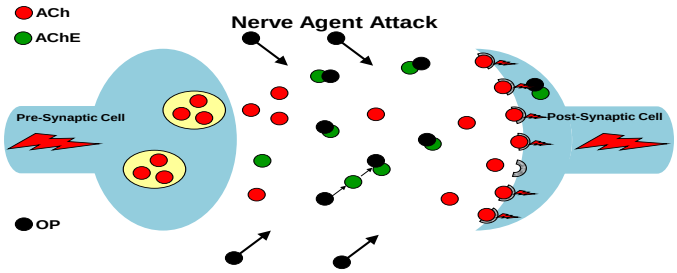


Figure 2. Synaptic Cleft with Nerve Agent Present (adapted from Fox, 2004:169)

After a period of time, which is different for each OP type, the OP-esterase bonds will mature by the de-alkylation of the OP (Cannard, 2006:89). Once matured, the bond between OP and esterase becomes irreversible and both the OP and the AChE are eliminated as active agents. The maturation process is known as aging. Once the aging process has occurred, AChE levels only recover through the production of new AChE. Regeneration of AChE is a slow process, occurring at a rate of approximately 1% per day (Siddel et al, 1997:137).

Nerve agents are OPs, esters of phosphoric acid which are commonly used in pesticides, flame retardants, lubricating oil additives, plasticizers, softeners and emulsifiers. Chemically, they are characterized by a central phosphorous atom bound to an oxygen atom, two alkyl groups and a leaving group (Cannard, 2006:88), Figure 3.

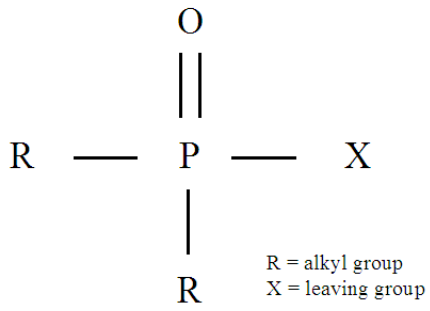


Figure 3. Basic Structure of Nerve Agent (Canard, 2006:87)

Contrary to popular belief, nerve agents are liquids, not gases, but they can be aerosolized or vaporized during an explosion (Cannard, 2006:87). Thus, the most common path of exposure is inhalation. This is also the most effective pathway due to the systemic distribution through the circulatory system. Symptoms typically peak within 15 to 30 minutes after exposure (Cannard, 2006:89).

Antidote Intentions

The three types of medication widely accepted for the treatment of nerve agent exposure are anticholinergics, oximes and anticonvulsants. The use and treatment using anticonvulsants will not be examined in this paper. A patient's recovery requires treatment within a few hours of exposure due to the bond that can form between organophosphates and AChE. After the aging process has occurred, only through the new production of AChE be restored, which could take months (Cannard, 2006:90).

Atropine is the typical anticholinergic used in the treatment of nerve agent intoxication. Atropine works by competitively and reversibly blocking Ach binding to the muscarinic receptor. The presence of atropine reduces the availability of muscarinic receptors for ACh (Cannard, 2006:92). This will lead to reduced secretion of exocrine glands and reduces over stimulation of smooth muscles (Cannard, 2006:92). Additionally, in high concentrations (those given to nerve agent victims) atropine may reduce and then block neuromuscular transmissions, possibly via pre- and postsynaptic mechanisms, in both receptor groups (Wali et al, 1987:587). Using atropine as a first line of defense against nerve agents has been widely accepted and has proven to reduce the mortality associated with the exposure to organophosphates (Karalliedde, 1999:1075). The military provides service members with auto injectors, such as the AtroPen in the Mark I kit. This kit contains 2 mg of atropine and is injected intramuscularly. The Center for Disease Control (CDC) recommends a dosage on the range between 2-6 mg, depending on the severity of the exposure. The body will naturally metabolize and excrete atropine overtime, however at high doses atropine can cause adverse health effects (USAMRICD, 2007:139).

While atropine can help alleviate or even reverse the effects of nerve agent intoxication, oximes help restore the function at the synaptic cleft. Oximes work by reactivating AChE that is bound by OPs. In essence the oximes pry the OP off the AChE. But oximes are only effective prior to the maturation or "aging" of the bond between OPs and AChE. The half-time aging for tabun, Sarin and VX is between 5 and 48 hours, while soman is only 2-6 minutes. For this reason oxime treatment is useless for patients exposed to soman (Cannard, 2006:90).

The oxime available in the U.S. is pralidoxime, commonly known as 2-PAM Cl. It can be administered either by intramuscular injection or intravenously. In order to counter the aging process it should be administered as quickly as possible to patients with moderate to severe exposure (Cannard, 2006:90).

Disparity in Treatment methods

While the general types of medications that are beneficial to victims of nerve agent exposure is generally universally accepted, the specific recommendations as to the dose and timing vary (Cannard, 2006:91). Acute poisoning with chemical weapons may induce severe toxicity, requiring immediate therapy, or even cause death. An obvious life-saving component of poisoning therapy is the use of specific antidotes. But evidence supporting the efficacy of antidotes in acute poisoning with chemical weapons is lacking (Szinicz et al, 2007:23). Since these types of poisonings are infrequent, compared to other forms, there has been little research interest by pharmaceutical companies to develop new antidotes, but also to confirm the effectiveness of those that are currently available. Hence, such antidotes are considered "orphan" drugs (Szinicz, 2007:24).

There exists a lack of evidence that supports how effective the current treatment methods for organophosphate exposure are (Szinicz, 2007:24). This is due in large part to the low incidence rate, but also to the ethics of testing human subjects with nerve agent exposure. In vitro studies have demonstrated the potential for oximes to be effective, but in actual practice they have proved to be less than effective and even potentially harmful (Szinicz, 2007:24).

The World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), and the New York Department of Health (NYDH) all have published guidelines for the treatment of nerve agent exposure. Each agency has different guidelines on the dose and timing of the dose to be administered (Cannard, 2006:91), Tables 2 and 3.

Table 2. Antidote recommendations for mild/moderate symptoms (CDC 2010, NYDH 2005, USAMRICD 2007)

		CDC (field)	CDC (hospital)	NYDH	USAMRICD (field)	USAMRICD (hospital)
Atropine	Initial Dose	2 – 4 mg	2- 4 mg	2 – 4 mg	2 mg	2 - 4 mg
	Repeat Dose	2 mg	2 mg	Not specified	2 mg	No instructions
	Repeat Interval	5 – 10 min	5 – 10 min	2 – 5 min	10 min	No instructions
Pralidoxime	Initial Dose	600 mg	1000 mg	600 mg	600 mg	600 – 1200 mg
	Repeat Dose	No instructions	No instructions	Not specified	600 mg	No instructions
	Repeat Interval	No instructions	No instructions	30 – 60 min, then hourly	10 min	No instructions

Table 3. Antidote Recommendations for Severe Symptoms
(CDC, 2010; NYDH, 2005; USAMRICD, 2007)

		CDC (field)	CDC (hospital)	NYDH	USAMRICD (field)	USAMRICD (hospital)
Atropine	Initial Dose	6 mg	6 mg	6 mg	6 mg	6 mg
	Repeat Dose	2 mg	2 mg	Not specified	Not applicable, only 6 mg carried in field	2 mg
	Repeat Interval	5 – 10 min	5 – 10 mg	2 – 5 min	Not applicable	3 – 5 min
Pralidoxime	Initial Dose	1800 mg	1000 mg	1800 mg	1800 mg	1800 mg
	Repeat Dose	No instructions	No instructions	Not specified	Not applicable, only 1800 mg carried in field	1000 mg
	Repeat Interval	No instructions	No instructions	30 – 60 min, then hourly	Not applicable	60 min

What this disparity in treatment has led to in the medical community is a lack of precise guidance. According to three medical doctors with a history in nerve agent poisoning, the treatment method is left to the discretion of the attending physician (Burns, Newmark, Casavant, personal communication, 14 April 2015). While no one would argue with a trained professional on this highly complex subject it would only seem logical that at least rudimentary guidelines exist for follow on treatment for someone who is exposed to nerve agents. Guidelines that should exist, if for no other reason than to deviate from.

The main area of concern that has been raised from previous studies is in the use of oxime in the treatment of nerve agent poisoning. These studies even doubt as to how effective it may be or suggest that it may be harmful (Eddleston et al, 2009:2). A randomized controlled study conducted by Eddleston and others challenged the efficacy of pralidoxime in organophosphate insecticide poisoning (Holder, 2011:21). The study compared the results of a group receiving the WHO recommended dose pralidoxime (WHO dosing mirrors that of the CDC) against a control group receiving a placebo. It

was noted that the oxime was successful at reactivating the AChE in the blood compared to no reactivation in the control group (Eddleston et al, 2009:4). However, despite the reactivation or potentially because of the reactivation of AChE the researchers found that the treatment resulted in a 69% increase in mortality (Eddleston et al, 2009:4). The conclusion from the study was that the dose of oxime recommended by the WHO is most likely to be ineffective and has the potential to be harmful (Eddleston et al, 2009:4). This could be in part because the dose level recommended by the WHO is based on level that is effective in in-vitro studies vice in-vivo studies (Eddleston et al, 2009:5). Based on these findings this research group recommended further study into the effects of oxime doses for use in humans as a treatment for nerve agent intoxication.

Physiologically Based Pharmacokinetic (PBPK) Modeling History on Organophosphate Treatment

The threat of the use of the nerve agents was formerly confined to the military field and hence easier to anticipate and treat. But events throughout the world have made this case unjust and thus not a viable option to consider. Due to this fact it is critical to evaluate medical interventions that may be effective in mass exposures when first responders and intensive care unit resources are likely to be overwhelmed. In such a situation, first responders should be able to administer specific first aid. In this situation antidotes that can be administered with auto injectors by the intramuscular route are particularly suitable. These antidotes should have a broad spectrum of action (e.g. active against various OP) along with minimal adverse effects, since they may be administered in panic situations without poisoning (Eyer et al, 2006:110). The question remains how to

test the efficacy of those antidotes according to the currently accepted “gold standard” of evidence-based medicine, without running into inevitable ethical conflicts (Eyer, 2006:110). This can be accomplished through physiologically based pharmacokinetic (PBPK) modeling.

PBPK modeling calculates the concentrations of chemicals over time in different tissues of the body, Figure 4. The model contains physiological properties such as tissue volume, blood flow rate and metabolic pathways. The model then applies mathematical constructs that allow the coordination of species–specific physiology, chemical-specific information, and the experimental protocol for the chemical or chemicals of concern. PBPK models aid scientists and decision makers to simulate the time-course concentration of chemicals in experimental animals and humans, to better determine estimates of actual chemical doses delivered to the target tissue, and thereby to provide a better prediction of response (Gearhart, 2009:791).

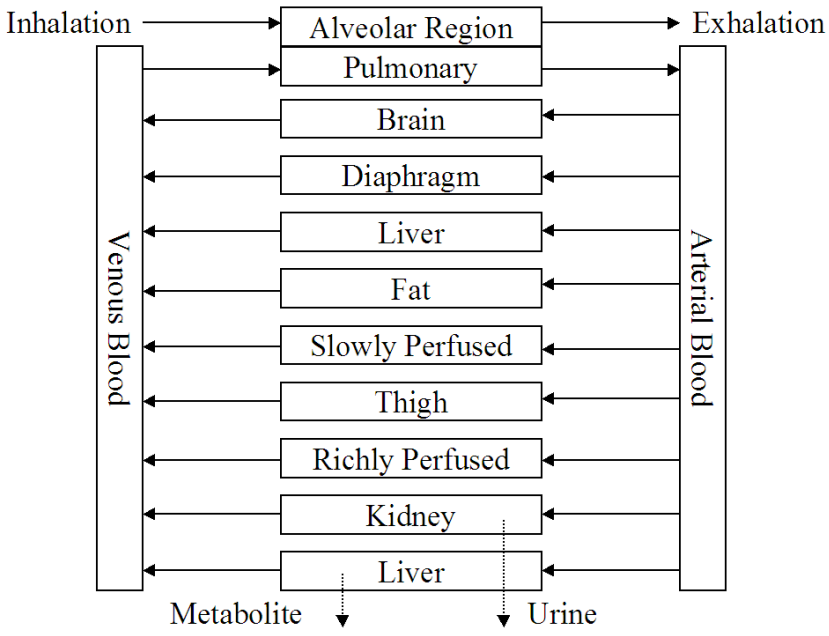


Figure 4. Basic PBPK Schematic (Gearhart et al, 1994)

Within the model, the organism under study is divided into discrete tissue compartments with similar physiological and pharmacokinetic properties (Hoang, 1995:101). Mass balance equations are created for each compartment to describe the concentration of the chemical in those compartments with respect to time. Within each compartment, binding and bio-transformation of the chemicals will affect the net accumulation rate of the chemical (Hoang, 1995:101). From this, ordinary differential equations are created to describe the alteration of chemicals to irrelevant byproducts through reaction with other chemicals and enzymes (Hoang, 1995:102).

Blood flow provides the medium through which the chemical is distributed. The product of the fraction of the blood flowing into each compartment, the concentration of the chemical (mass/volume), and the cardiac output (volume/time) determines the amount of chemical entering the compartment (mass/time) (Seaman, 2008:24). A partition coefficient is used to describe the diffusion of the chemical from the tissue compartment into the venous blood flow. The amount of chemical leaving a compartment (mass/time) is equal to the product of the fraction of blood flow from the compartment, the cardiac output (volume/time), the concentration of the chemical in the tissue compartment (mass/volume), and the inverse of the tissue/blood partition coefficient (Seaman, 2008:25). The compartment coefficient is directly related to outflow: a higher coefficient equates to slower outflow.

The use of PBPK modeling to estimate the effects of OPs on the human body can be traced back to a study conducted by Maxwell and others in 1987. This particular study looked at the inhibition of cholinesterase by soman in various organs and plasma of rats. During this study the researchers used a multiple regression model to determine the

extent of cholinesterase inhibition (Holder, 2011:23). From this model it was determined that blood flow, carboxylesterase and cholinesterase accounted for 94% of the variability (Maxwell et al, 1987:71). Blood flow accounted for 79% of the variations, leading to the conclusion that a PBPK model could be used to model the kinetics of soman on in-vivo cholinesterase inhibition (Maxwell et al, 1987:72).

Gearheart and others took PBPK modeling to the next step in 1994. They developed a model for organophosphate exposure and AChE inhibition in humans. The group developed a model to look at two different organophosphates, DFP (an insecticide known as diisopropylfluorophosphate) and parathion. The model parameters were derived from in-vivo data from rats and then scaled to humans. The models were validated by comparing the data collected from the simulation to literature obtained from exposure to these chemicals (Holder, 2011:26). The conclusion reached was that this type of model could be used for various types of organophosphates (Gearhart et al, 1994:58).

In 2002 Timchalk and others developed a PBPK model for chlorpyrifos, the active ingredient in some commercially available pesticides. This study used experimental data from rats and humans exposed to chlorpyrifos along with literature to construct a model that exhibited the behavior seen in experimental trials (Holder, 2011:26). Since the model constructed was capable of describing human and rat response to chlorpyrifos from acute and chronic exposure to a good degree it was concluded that a PBPK model would be a good starting point for other organophosphate models (Timchalk et al, 2002:35).

Worek and others created a model to demonstrate the effectiveness of different oximes in nerve agent exposure. The team built a model to look at the effectiveness of the three types of oximes (obidoxime, oxime and HI6) in response to exposure to Sarin, CycloSarin and VX (Holder, 2011:23). The model was verified by comparing the AChE levels predicted by the model to in-vivo levels measured in a patient poisoned by parathion and treated with atropine and obodoxime (Holder, 2011:23). From data gathered from the model it was determined that the model would be capable of comparing various oximes, determining effective oxime concentrations, and for developing oxime treatment for organophosphate poisoning (Worek et al, 2005:195).

In 2008 Seaman and in 2011 Holder continued the use of PBPK modeling to describe the behavior associated with organophosphate exposure and develop specific treatment recommendations. Seaman's research aimed at determining the effectiveness of the atropine and oxime doses and timing under current prescribed requirements. He concluded that oximes were more effective when used against less toxic organophosphates, but less effective, or even deadly, when organophosphates had a very high toxicity (Seaman, 2008:52). Holder, using Seaman's work as a starting point concluded that the use of oximes against strong organophosphates, such as nerve agents, is ineffective and has the potential to increase the severity of symptoms (Holder, 2011:56). Additionally, he used the data obtained from the model to develop an optimal dosing strategy that varies significantly from the currently prescribed guidance.

III. Methodology

Model Configuration

In order to facilitate the functionality of the PBPK model simulations were performed using Stella 10.0.5 numerical integration software. The model was configured such that compartments for the pulmonary, arterial, venous, brain, diaphragm, liver, fat, slowly perfused, richly perfused, thigh and kidney tissues were created. The model configuration describing absorption, distribution, metabolism and excretion was based largely on the model developed by Gearhart and others in 1994. The model used for this simulation process also depicts the behavior of ACh, AChE, BuChE and carboxylesterase in the compartments previously described. The model structure is illustrated in Figure 4.

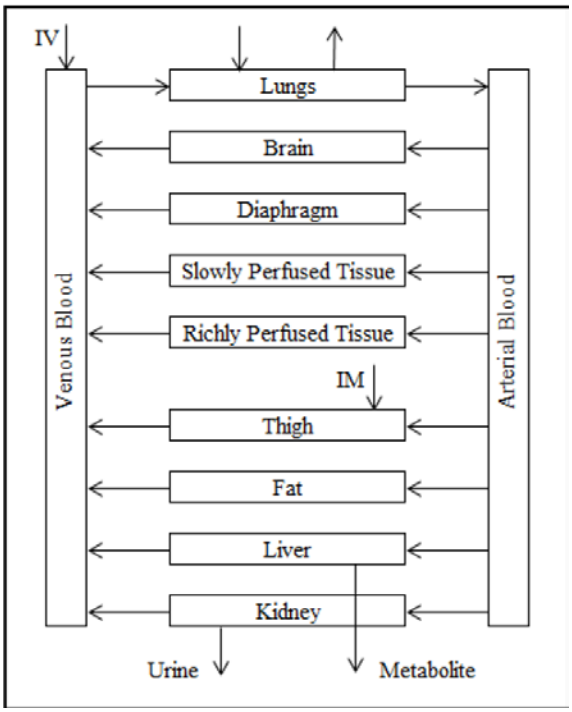


Figure 5. PBPK Schematic (Seaman 2008:31)

The model portrays organophosphate absorption through inhalation into the pulmonary tissue and then distributed through the rest of the system through arterial

blood flow. Atropine and oxime are introduced via intramuscular injection in the thigh or through intravenous means. These two compounds are then eliminated by metabolism via enzymes in the liver or excreted in the urine through the kidneys. ACh and esterase were produced and degraded in each of the different tissue compartments as well. The reactions between enzymes and chemicals entering the body occurred within each of the previously described compartments with the exception of the fat compartment. Since esterase concentrations were assumed to be negligible or non-existent in fat tissue no reaction was simulated in the fat compartment (Seaman, 2008:32). Additionally, degradation of OPs and esterase occurred by maturation of the organophosphate-esterase bond. Due to the buildup of acetylcholine in the postsynaptic membranes, synapses are kept in a permanent state of stimulation. With the muscles unable to return to their natural resting state the most basic of functions are impaired or completely disabled. The most crucial of all of these functions is respiration. Without the natural respiratory contraction and relaxation the body is deprived of oxygen. Since respiratory failure is the leading cause of death in nerve agent victims the diaphragm was singled out as the compartment within the PBPK model to track for symptoms.

Equations

A complete list of equations used is provided in Appendix A. The PBPK model works on the premise of a mass balance equation with reactions taking place in each compartment between the enzymes and chemicals introduced. The equation for this reaction is shown in equation 1.

$$\text{Accumulation} = In - Out + Generation - Consumption \quad (1)$$

Flow into the system of the chemical agent is achieved through inhalation while treatment for the symptoms is achieved through intramuscular injection or intravenous flow into the venous tissue. Outflow from the system is through exhalation, urination and metabolism. The generation and consumption in the compartments occurs through natural synthesis as well as degradation and chemical reactions between different components. The natural synthesis of esterase was zero order and represented by a synthesis constant. Degradation of esterase was represented by a first order process and was dependent on the esterase concentration within the compartment (Holder, 2011:31). The concentration of esterase in each compartment is shown in equation 2.

$$\frac{d(Esterase)}{dt} = Synthesis\ constant - Degradation\ constant * (Esterase) \quad (2)$$

The reaction between the organophosphate and the esterase is shown in equation 3.

$$\frac{d\left(\frac{Esterase}{OP}\right)}{dt} = \mathrm{ki(Esterase)(OP)} - \mathrm{ks}\left(\frac{\mathrm{Esterase}}{\mathrm{OP}}\right) - \mathrm{ka}(\frac{\mathrm{Esterase}}{\mathrm{OP}}) \quad (3)$$

For the previous equation the values of k are defined as:

k_i= OP reaction rate coefficient with esterase ($mol^{-1}time^{-1}$)

k_a= OP esterase complex aging reaction rate coefficient ($time^{-1}$)

k_s= OP esterase complex natural separation reaction rate coefficient ($time^{-1}$)

The chemical reaction between the organophosphates and the esterase with oxime is shown in equation 4.

$$\frac{\mathrm{d}\left(\frac{\mathrm{Esterase}}{\mathrm{OP}}\right)}{\mathrm{dt}} = -kr\left(\frac{Esterase}{OP}\right) Oxime \quad (4)$$

kr= OP esterase complex reaction rate coefficient with oxime ($mol^{-1}time^{-1}$)

The interaction between ACh, AChE and atropine is shown in equation 5 (Seaman, 2008:34).

$$\frac{\mathrm{d(active\ ACh)}}{\mathrm{dt}} = p1\left(\frac{p1}{(p2+atropine)}\right) - p2(AChE)(active\ ACh) \quad (5)$$

When atropine is not present the equation simplifies to equation 6.

$$\frac{d(active\ ACh)}{dt} = p1 - p2(AChE)(active\ ACh) \quad (6)$$

p1=ACh binding rate (mass/time)

p2=ACh degradation constant (time^{-1})

In order to determine the effectiveness of the treatment an individual is receiving the model applies a symptom tracking value. This symptom value is used to track the severity of symptoms as well as the effectiveness of the treatment being received. It is the ratio of the concentration of the ACh molecules that are actively stimulating the nerves over the basal concentration of active ACh molecules. At homeostasis the value is one. When an OP is introduced the ability of AChE to break down ACh is inhibited, thus overstimulation occurs and the symptom value to a value greater than one. Hence, the greater the symptom value in the model, the more severe the symptoms. The equation for the output of the symptom line is shown in equation 7.

$$\frac{d(Symptoms)}{dt} = \frac{ACh\ site}{(Basal\ ACh\ Site)} \quad (7)$$

To quantify the symptom value and establish when symptoms first appear and when death transpires, values were taken from the literature. According to Siddel and others levels at 10% inhibition would produce mild symptoms, but not to the level that would require medical attention. Levels above 25% inhibition would require treatment (Siddel et al, 1997:139). Further guidance is provided by Ashani and Pistinner who state that when 90% inhibition occurs death is imminent (Ashani and Pistinner, 2004:365). For the purpose of the symptom value, 10% equates to 1.10 which would be very mild

symptoms, 25% is 1.25 for the symptom value which would be moderate symptoms that would require some treatment, and 1.90 would be the level at which death occurs.

The only way medical personnel can determine the severity of exposure is through visually discerning the clinical signs of the patient. The Agency for Toxic Substance and Disease Registry (ATSDR) has developed triage procedures for nerve agent causalities, Table 4. A value of 1.25 for the symptom value would refer to someone experiencing minimal symptoms and would be triaged with a priority of three. Likewise 1.90 would be someone that is expectant.

Table 4.Triage Protocol for Nerve Agent Causalities (ATSDR, 2014)

Category (Priority)	Effects	Clinical Signs
Immediate (1)	Unconscious, talking but not walking, or moderate to severe effects in two or more systems (e.g., respiratory, GI, muscular, CNS)	Seizing or post-ictal, severe respiratory distress or apneic. Recent cardiac arrest.
Delayed (2)	Recovering from agent exposure or antidote	Diminished secretions, improving respiration.
Minimal (3)	Walking and talking	Miosis, rhinorrhea, mild to moderate dyspnea.
Expectant (4)	Unconscious	Cardiac/respiratory arrest of long duration.

The rationale behind the triage of individuals exposed to a nerve agent in a mass causality event would be based on symptoms as well as antidote supplies available. Individuals displaying minimal symptoms would not be treated at the scene, but would be labeled as minimal and sent to the nearest hospital. The administration of atropine would most likely not be given to someone displaying these types of symptoms simply based on the fact that they are not in dire need of treatment to alleviate the symptoms. The

antidotes would only be given to those suffering from the most severe symptoms with a likelihood of survival.

The symptom level is directly related to the exposure level. According to the U.S. Army Medical Research Institute of Chemical Defense (USAMRCD) the levels of exposure are moderate (MCT), incapacitating (ICT) and lethal (LCT). The concentrations of these levels are listed in Table 5.

Table 5. Vapor Toxicity (mg-min/m^3) (USAMRCD, 2007:129)

Agent	LCT_{50}	ICT_{50}	MCT_{50}
GB(Sarin)	100	75	3

The term C*t* is used to describe an estimate of dose. C represents the concentration of the substance (as vapor or aerosol) in air (usually expressed as mg/m^3) and *t* represents time (usually expressed in minutes). The C*t* value is the product of the concentration (C) to which an organism is exposed and multiplied by the time (*t*) during which it remains exposed to that concentration (Siddel et al, 1997:142).

Assumptions

In attempt to mimic the functions of the human body several assumptions were made in the model. First, the model assumes instantaneous mixing and equilibrium of the different chemicals within each of the compartments. Second, metabolism of chemicals follows Michaelis-Menten kinetics. And lastly, the release of acetylcholine from the pre-synaptic nerve cell and diffusion of the neurotransmitter across the synaptic cleft is assumed to be instantaneous and continuous.

Generation and degradation of AChE is considerably slower than is represented in this model. AChE regeneration occurs at a rate of 1% per day (Siddel et al, 1997:137). Due to the extremely slow nature of this regeneration, the parameters for AChE regeneration were modified to show a more exaggerated version of regeneration in order to demonstrate the nature of the symptoms over a timeline that is applicable to emergency room physicians.

Parameters and Coefficients

Parameters and coefficients for this model were obtained from literature or were retained from the Seaman model of 2008. Sarin data was obtained from a 2005 PBPK model constructed by Gearhart. The partition coefficients and metabolic parameters applied in this model provided antidote results that mimicked the observations seen by Gearhart in his model. A full list of the parameters and coefficients used can be found in Appendix B. In addition to the aforementioned parameters a kidney elimination constant of 0.35 was used to produce reasonable elimination results that might be expected from urine excretion.

The additional values listed in the model to include synthesis rate, and basal levels were obtained from Gentry and others (Gentry el al, 2002:122). The degradation constants were obtained from the Seaman model of 2008.

Simulation Protocol

The simulation was broken down into two specific phases. The first phase was verification. During these simulations the intent was to verify the model was producing accurate results according to current treatment guidelines as prescribed by the Center for

Disease Control (CDC) and the U.S. Army. The therapeutic strategies are broken into two exposure groups, moderate and incapacitating as defined by the Army. The intended treatment method for both of these obviously varies, but is solely based on symptoms displayed by the victim.

To verify the model, exposure time remained consistent at 15 minutes. The exposure started at 5 minutes into the simulation time window and ended at 20 minutes. Time until treatment was administered varied between 5, 10 and 15 minutes from the start of the simulation. These timing seemed appropriate for the amount of time it would take until treatment would be rendered. For each simulation the concentration of Sarin and duration of exposure (C_t) were recorded as well as time until treatment, amount of antidote given and the symptom level. For this set of simulations atropine and pralidoxime were administered intramuscularly at the level currently prescribed by the CDC and the Army. For the moderate symptoms a dose of 2 mg of atropine and 600 mg of pralidoxime was simulated. For the more severe symptoms 6 mg atropine and 1800 mg of pralidoxime was simulated. With the prescribed dosing administered the symptom level was tracked to verify effectiveness of dosing. Maximum symptom levels and increase or decrease of symptoms was recorded after each simulation.

The second set of simulations examined a scenario in which a victim was exposed to a relatively low concentration of Sarin and they were displaying moderate symptoms. The assumption for this scenario is that an individual would be triaged out of the hot-zone and taken to a local hospital or military aid station for follow on treatment with only oxime being administered. The timing for the administration was simulated at 30, 45 and 60 minutes. With the dosing strategy not clearly defined the assumption was made that

the attending physician may prescribe a prophylactic dose of oxime. The dosing was simulated at 600 mg and then again at 200 mg in order to determine the effects oxime therapy would render on an individual displaying moderate symptoms.

IV. Results and Discussion

A complete list of results achieved for each exposure scenario and treatment applied can be found in Appendix C. Only simulations found to be most relevant are presented in this section with a graphical depiction. This section is divided into two segments: Model Verification and Test for Re-bound of Symptoms.

Model Verification

The model was verified against current treatment protocols that correspond to the type of symptom level observed to demonstrate that the model is behaving as expected against scientifically verified parameters. Without proper verification any simulations that were produced would be met with skepticism regarding the validity of the model. The intent is to prove that the model is behaving as closely as possible to a human body when exposed to Sarin gas and the treatment protocol prescribed is effective in alleviating symptoms.

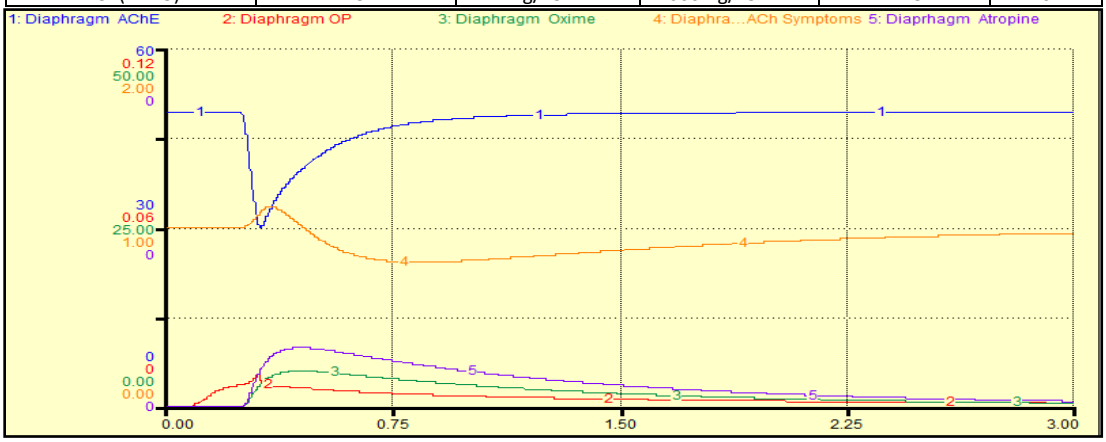
Due to the fact that the lethality of these agents is known and someone exposed to these levels would be considered expectant simulations using this level of toxicity was not applied. For simulation procedures the model was verified against a moderate exposure (MCT) and an incapacitating exposure (ICT). These levels of exposure are defined by the U.S. Army. The MCT is any exposure up to 1.5 C_t and the ICT was anything above a C_t of 1.75. In order to properly run a model based on mathematical equations correct parameters are invaluable. However, when dealing with actual victims the concentration one is exposed to will not be known. That is why it is more important to focus on the symptom level.

The treatment applied for MCT was 2 mg atropine and 600 mg oxime given via intra-muscular injection at time intervals of 15, 20 and 30 minutes into the simulation. Values graphically displayed are the following: 1. Active AChE levels, 2. Active OP, 3. Oxime levels, 4. Symptom line, 5. Atropine levels. These times were chosen based on the assumption that it would take at least those times for someone to receive any treatment. The ICT followed the same time intervals, but the dosing was increased to 6 mg atropine and 1800 mg oxime. The dosing strategies are based on CDC and U.S. Army protocol.

1) Simulations 1a, 1b, 1c (MCT): These three simulations tested a very low C_t, 1.5, with a treatment of both atropine and oxime given at the aforementioned times and the dosing prescribed for mild symptoms. The symptom line, #4 on the graph, rises as soon as the Sarin gas is introduced and the AChE levels, line #1, drop accordingly. As previously mentioned the AChE recovery would not be as rapid as portrayed in this model, but due to the compressed timeframe intended to be illustrated by this model recovery happens faster.
    a) Administered at 15 minutes: With treatment being administered at 15 minutes into the simulation the symptom level is fairly low, only reaching a maximum of 1.15 on the symptom line. With such a low symptom level it is debatable wither or not treatment would be given. But, to demonstrate that the model is behaving appropriately it was simulated. With such a mild symptom level the treatment pushes the symptom line below 1. This is due to the action of the atropine blocking receptor sites and the potential of producing negative results with such a mild exposure. Although not life threatening the values less than one on the symptom line would be rapid heartbeat, nausea, dizziness, and lack of sweating.

Figure 6. Simulation 1a, Moderate Symptoms, Treatment at 15 minutes

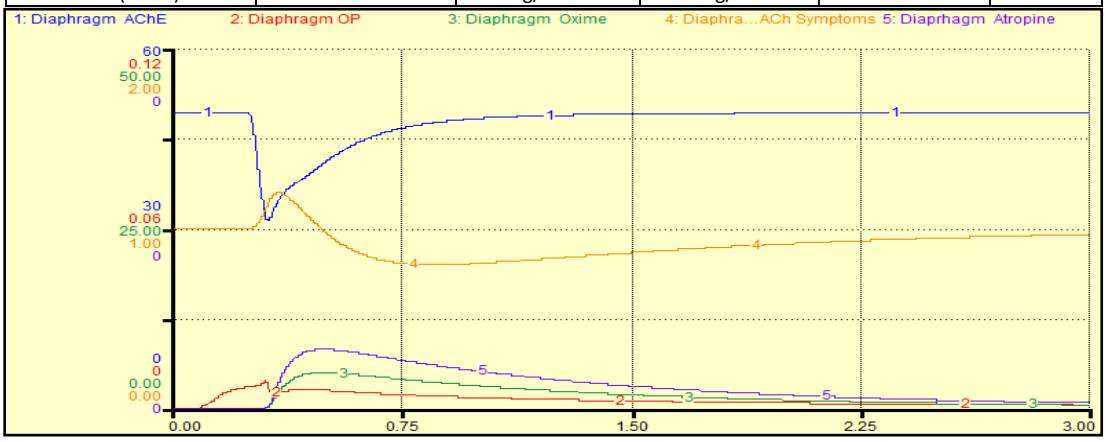
Ct(concentration*time)	ExposureTime (Minutes)	ATROPINE DOSE/Time	OXIME DOSE/Time	Symptom Level Max.	Rebound Symptom Max.
1.5=(.1*15)	15	2mg/15 min	600mg/15min	1.15	0



b) Administered at 20 minutes: The symptom line reaches a maximum of 1.2 vice 1.15 for the previous simulation. This would be expected since time until treatment increased by 5 minutes. The gas has longer time to work its effects on the body. Again, AChE levels drop as soon as Sarin is introduced but rebounds once oxime and atropine are applied. Similar to the last simulation the symptom line drops below 1 due to the mild exposure.

Figure 7. Simulation 1b, Moderate Symptoms, Treatment at 20 Minutes

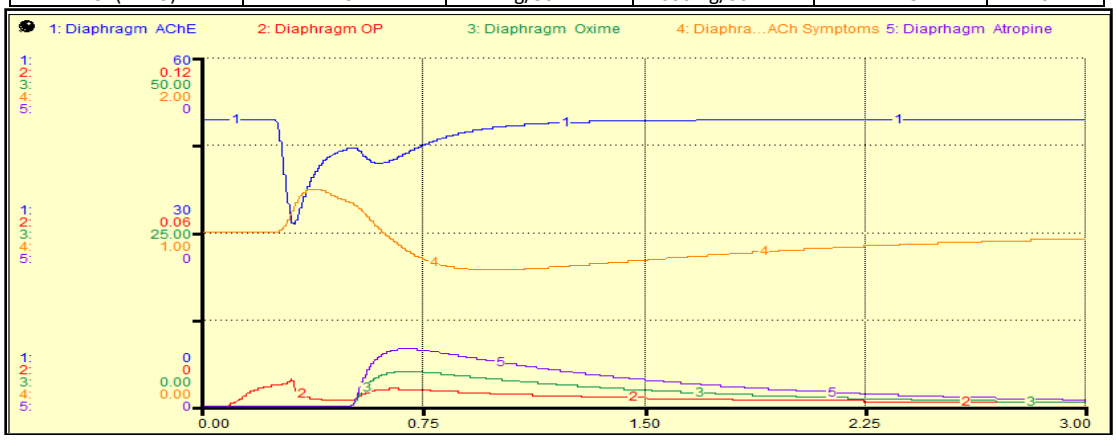
Ct(concentration*time)	Exposure Time (Minutes)	ATROPINE Dose/Time	OXIME Dose/Time	Symptom Level Max.	Rebound Symptom Max.
1.5=(.1*15)	15	2mg/20 min	600mg/20 min	1.2	0



c) Administered at 30 minutes: Only difference from the previous two simulations is the time until the treatment is applied, 30 minutes post exposure. Accordingly, the symptom line reaches a maximum of 1.25, higher than the previous two which would be expected. A significant note on this simulation is the drop in AChE levels once the atropine and oxime are introduced. This is suspected to be the resurgence of bound Sarin caused by the introduction of the oxime. The oxime breaks the bond between the Sarin and AChE, thus releasing more unbound Sarin into the system. However, the symptom line tracks accordingly and begins to return to the natural state.

Figure 8. Simulation 1c, Moderate Symptoms, Treatment at 30 Minutes

Ct(concentration*time)	Exposure Time (Minutes)	ATROPINE DOSE/Time	OXIME DOSE/Time	Symptom Level Max.	Rebound Symptom Max.
1.5=(.1*15)	15	2mg/30 min	600mg/30 min	1.25	0

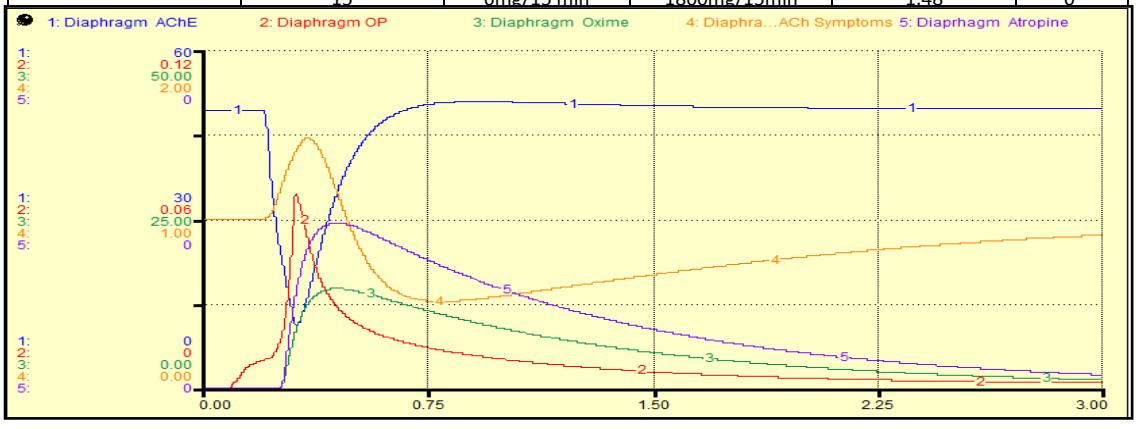


2) Simulations 2a, 2b, 2c (ICT): The C_t was raised to 2.25 for these next three simulations and accordingly the dosage was increased to the prescribed amount, 6 mg atropine and 1800 mg oxime.

   a) Administered at 15 minutes: As would be expected the symptom line reached a level that would be considered incapacitating, 1.48. Likewise once the exposure began the AChE levels dropped. Once treatment was administered the symptom line began to gradually approach steady state. Thus proving that the treatment is effective.

Figure 9. Simulation 2a, Incapacitating Symptoms, Treatment at 15 Minutes

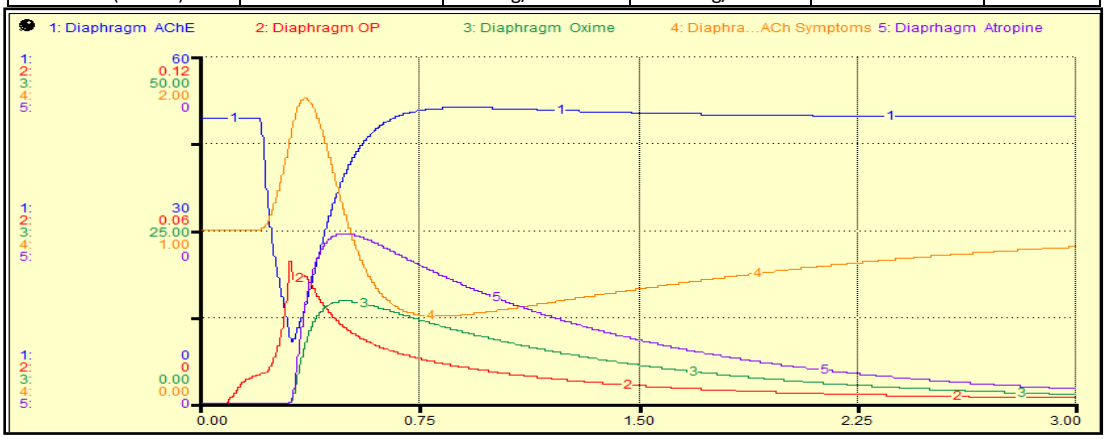
Ct(concentration*time)	ExposureTime (Minutes)	ATROPINE DOSE/Time	OXIME DOSE/Time	Symptom Level Max.	Rebound Symptom Max.
2.25=(.15*15)	15	6mg/15 min	1800mg/15min	1.48	0



b) Administered at 20 minutes: The symptom line reached a maximum of 1.75 due to the fact that treatment was not administered until 20 minutes. Similarly the AChE levels dropped in response to the exposure to a level considerably lower than the MCT scenario. This would be expected because the concentration is greater. Treatment was effective as shown by the symptom line approaching steady state.

Figure 10. Simulation 2b, Incapacitating Symptoms, Treatment at 20 Minutes

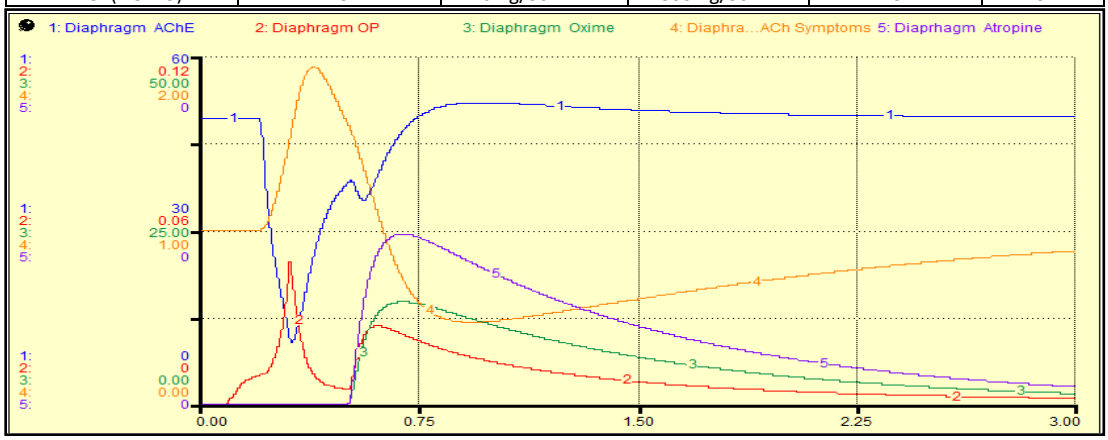
Ct(concentration*time)	ExposureTime (Minutes)	ATROPINE DOSE/Time	OXIME DOSE/Time	Symptom Level Max.	Rebound Symptom Max.
2.25=(.15*15)	15	6mg/20 min	1800mg/20 min	1.75	0



c) Administered at 30 minutes: With the C_t remaining constant but the time until treatment applied extended out to 30 minutes the symptom line reached a maximum value of 1.94. With 1.90 being the maximum tolerable limit for symptoms this threshold was crossed and the victim would have expired.

Figure 11. Simulation 2c, Incapacitating Symptoms, Treatment at 30 Minutes

Ct(concentration*time)	ExposureTime (Minutes)	ATROPINE DOSE/Time	OXIME DOSE/Time	Symptom Level Max.	Rebound Symptom Max.
2.25=(.15*15)	15	6mg/30 min	1800mg/30 min	1.94	0



Test for Re-Bound in Symptoms

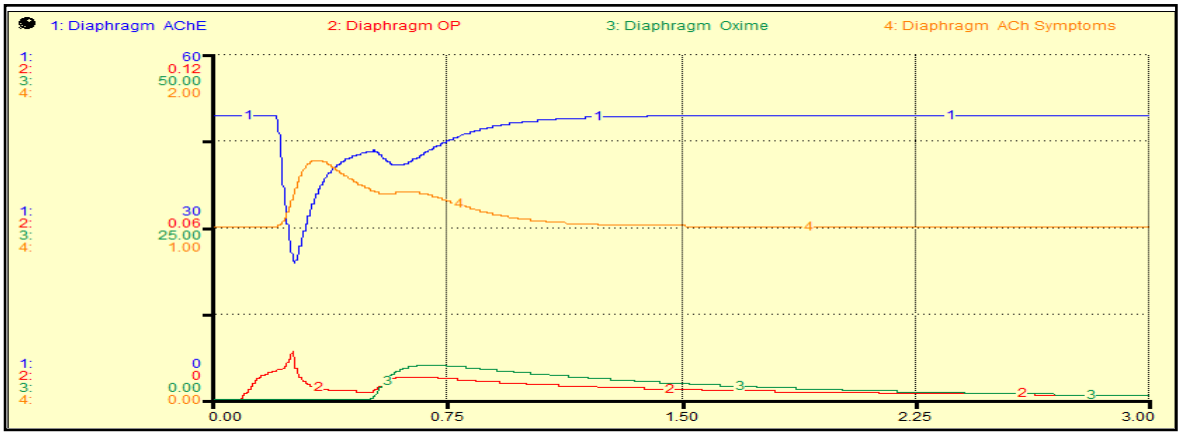
With the model verified it was time to test the hypothesis that the administration of oxime alone to victims suffering from mild exposure levels may increase the symptoms. Nine simulations were run all with symptom levels at 38% inhibition of ACh, equating to a symptom value of 1.38. All simulations were run with treatment being administered at 30, 45 and 60 minutes after initial exposure using the treatment protocol prescribed by the CDC and U.S. Army for mild exposure victims. These times were chosen based on the fact the individuals displaying less severe symptoms would not be treated in the hot-zone. They would be triaged and then sent off to a medical center to be evaluated and treated. With the treatment protocol being at the discretion of the physician to treat symptoms to alleviate suffering only oxime therapy might well be a plausible avenue of approach.

3) Simulations 3a, 3b, 3c (600mg Intra-Muscular Oxime):

a) Administered at 30 minutes: Symptom level rebounded by .01. While not a significant increase it still does represent an increase in symptom level when symptoms were starting to diminish naturally through the course of time. However, the symptom level did return to steady state fairly quickly after the administration of oxime, proving that while not detrimental to recovery the effectiveness in speeding recovery is questionable at this stage of the simulations.

Figure 12. Simulation 3a, 600mg Oxime IM at 30 Minutes

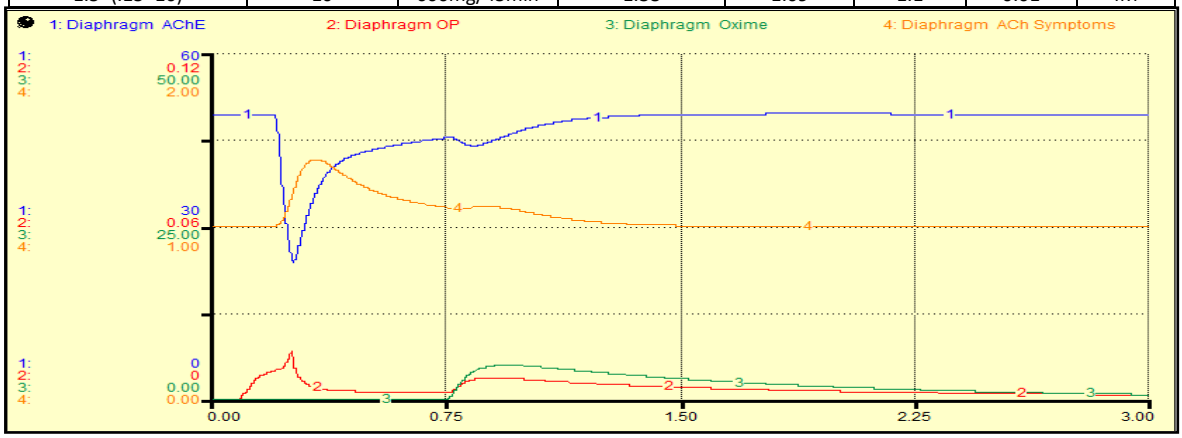
Ct (concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	600mg/30min	1.38	1.21	1.22	0.01	IM



b) Administered at 45 minutes: With the treatment delayed even further the natural recovery process of the body brought the symptom line down from 1.38 to 1.09, but as soon as oxime was administered the level rebounded to 1.1. Again, not a dramatic increase in symptoms, nonetheless an increase.

Figure 13. Simulation 3b, 600mg Oxime IM at 45 Minutes

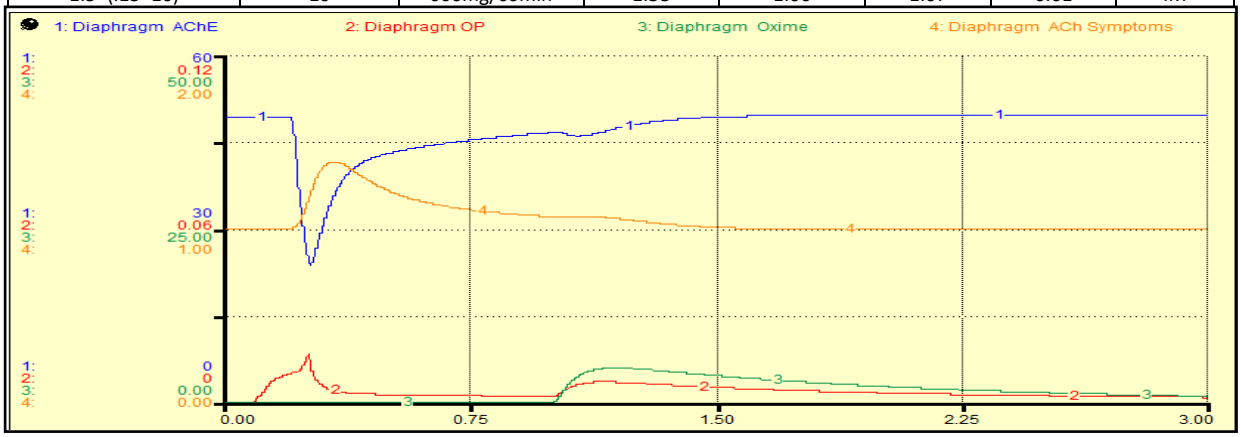
Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	600mg/45min	1.38	1.09	1.1	0.01	IM



c) Administered at 60 minutes: Even after an extended period of time, 60 minutes, without treatment a slight increase in the symptom line was recorded. The symptom line naturally recovered to 1.06 and then rebounded to 1.07 when oxime was administered. While these symptoms levels most likely would not require treatment of any kind, the proof still remains that symptom levels increased when oxime was applied.

Figure 14. Simulation 3c, 600mg Oxime IM at 60 Minutes

Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	600mg/60min	1.38	1.06	1.07	0.01	IM

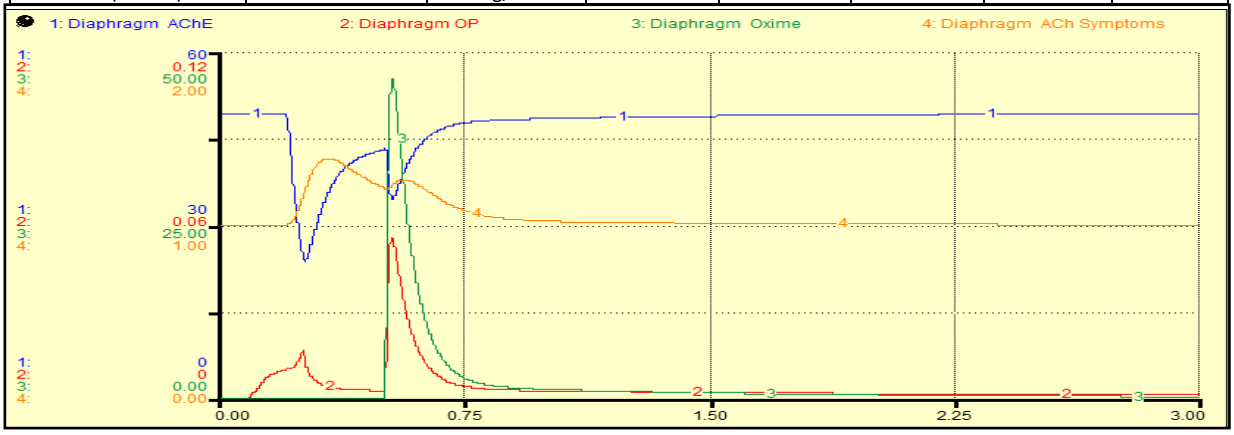


4) Simulations 4a, 4b, 4c (600mg Intra-Venous Oxime): These simulations start the use of intra-venous administration of oxime therapy applied at the same time intervals as the previous simulations.

a) Administered at 30 minutes: The symptom level rebounded the most significantly in this scenario. From a low of 1.21 back up to 1.26. With the oxime hitting the system faster and at a higher concentration it enabled the release of bound Sarin to be re-released into the system to cause its damaging effects. At 30 minutes the levels of bound Sarin in the system would still be relatively high thus causing a significant spike in symptoms.

Figure 15. Simulation 4a, 600mg Oxime IV at 30 Minutes

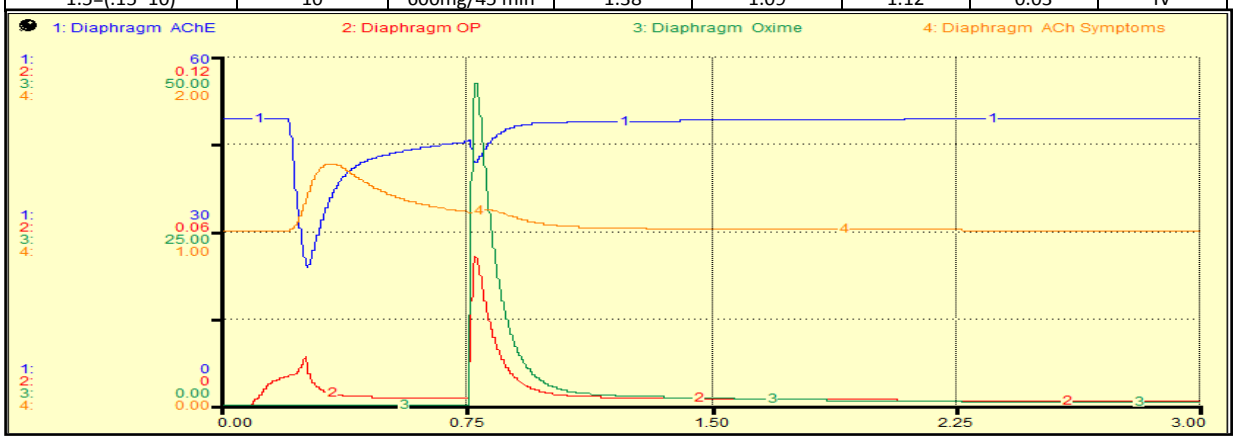
Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	600mg/30 min	1.38	1.21	1.26	0.05	IV



b) Administered at 45 minutes: As time moves away from exposure and oxime is administered the symptom rebound starts to decrease.

Figure 16. Simulation 4b, 600mg Oxime IV at 45 Minutes

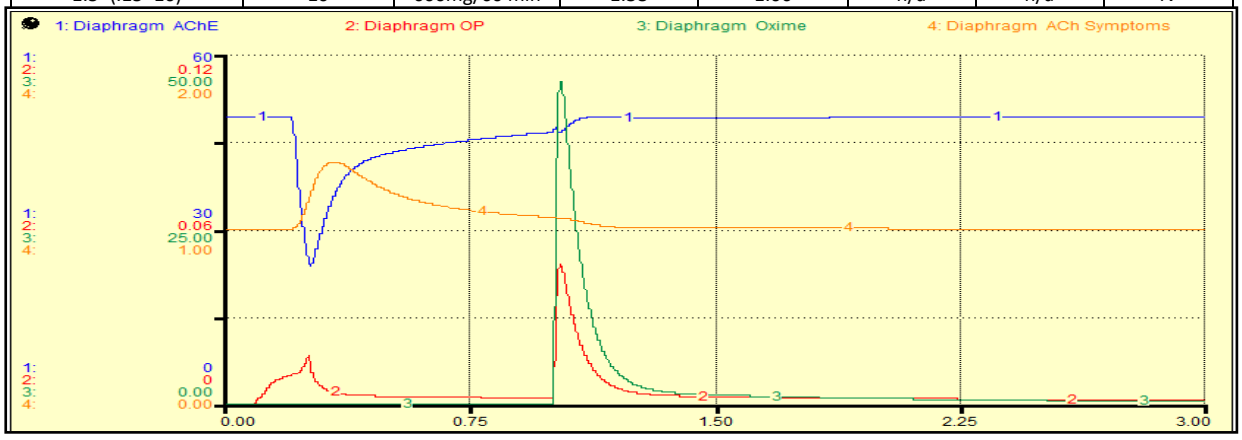
Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	600mg/45 min	1.38	1.09	1.12	0.03	IV



c) Administered at 60 minutes: No rebound in symptom observed when treatment was delayed out to 60 minutes. The natural degradation process has had time to work and alleviate symptoms.

Figure 17. Simulation 4c, 600mg Oxime IV at 60 Minutes

Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	600mg/60 min	1.38	1.06	n/a	n/a	IV

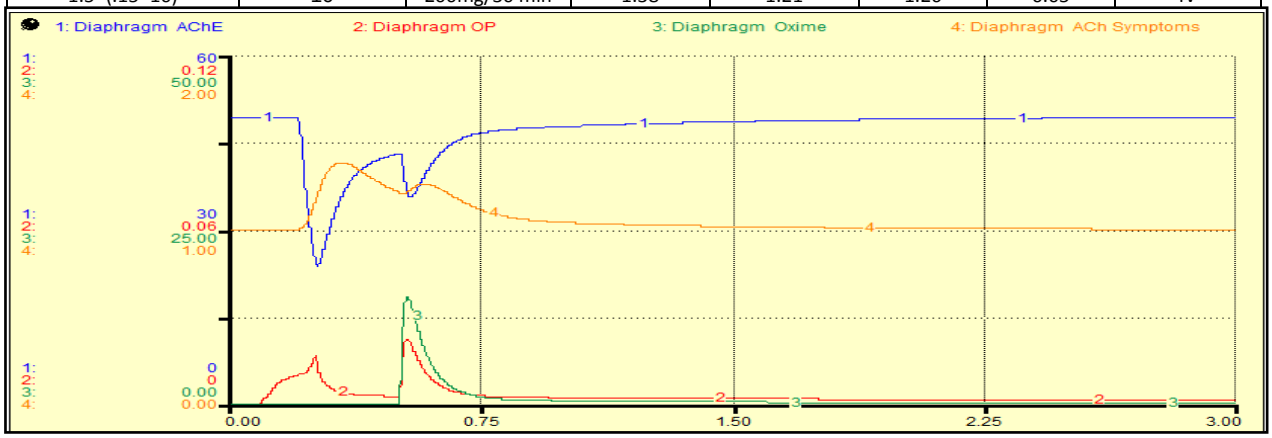


5) Simulations 5a, 5b, 5c (200mg Intra-Venous Oxime): In order to draw an accurate conclusion as to whether oxime therapy was beneficial or detrimental the dosing of oxime was lowered to 200 mg with the same time frame for administration. The results for the lower dose mirror that of the 600 mg intra-venous treatment.

a) Administered at 30 minutes: Symptom levels rebounded by .05, while AChE levels dropped at the same time and the same level as they did with the 600 mg application.

Figure 18. Simulation 5a, 200mg Oxime at 30 Minutes

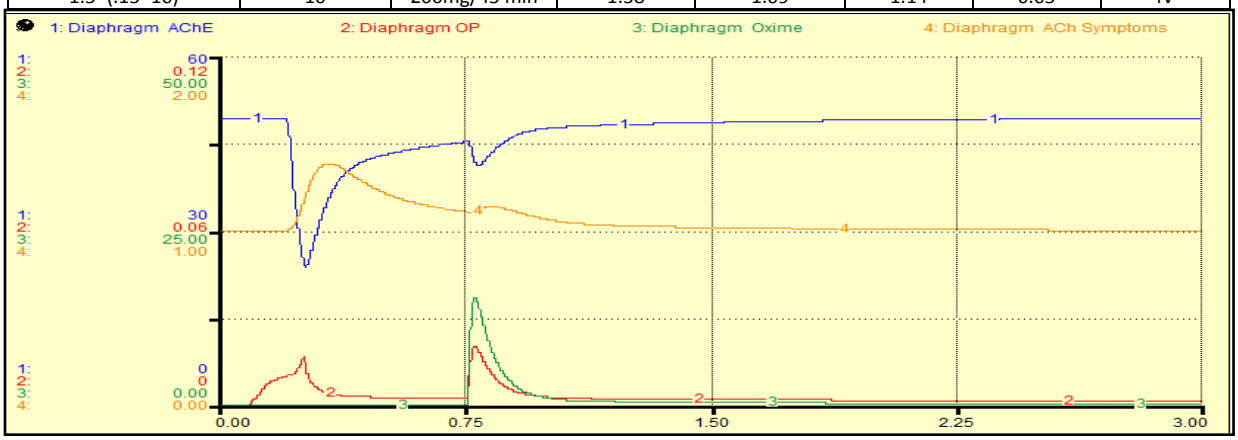
Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	200mg/30 min	1.38	1.21	1.26	0.05	IV



b) Administered at 45 minutes: Symptom levels rebounded by .05, thus proving that even at a lower dose the use of oxime can produce contrary results.

Figure 19. Simulation 5b, 200mg Oxime at 45 Minutes

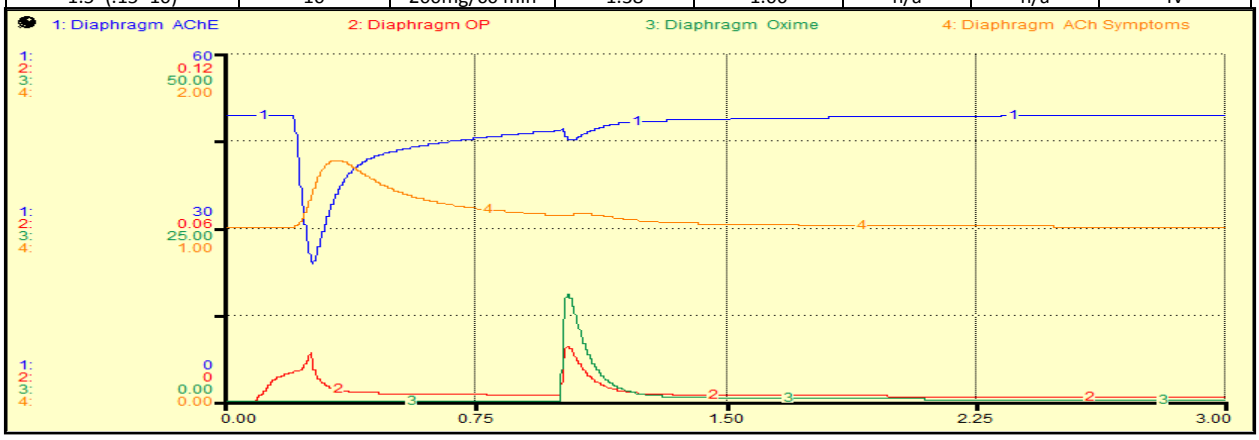
Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	200mg/45 min	1.38	1.09	1.14	0.05	IV



c) Administered at 60 minutes: As previously demonstrated the symptom level dropped to a level that would not be recognizable. Oxime therapy was still applied and no increase in symptom levels was recorded.

Figure 20. Simulation 5c, 200mg Oxime at 60 Minutes

Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
1.5=(.15*10)	10	200mg/60 min	1.38	1.06	n/a	n/a	IV



V. Conclusion

With the relative ease in which nerve agents are made, the vast quantity that exist throughout the world and the horrific potential they wield the possibility of an attack on a military or civilian population seems inevitable. The potential loss of life and suffering would be staggering and on a scale not frequently witnessed. But with proper procedures in place the losses can be mitigated. Employing the procedures set forth by the CDC and U.S. Army the vast majority of exposed patients that arrive at a hospital will survive. However, the key to survival will be in the triage procedures and the follow on care provided with limited resources.

The key to the survival of the individuals suffering from the most grave of symptoms is the expedient treatment with antidotes (atropine and oxime) that may well be in short supply. By administering these crucial drugs in the prescribed dosing to only those individuals who truly need it will inevitably save lives and reduce suffering. But administering these drugs, specifically oxime, to victims displaying moderate symptoms does not alleviate symptoms and potentially robs that drug from someone who could benefit from it.

The overall conclusion reached in this research is as follows:

- The current nerve agent treatment protocol prescribed by the CDC and U.S. Army is effective in saving lives for those victims experiencing incapacitating symptom.
- Oxime therapy alone given to those victims experiencing mild symptoms is not effective. The recommended treatment for these individuals would be no oxime therapy administered and potential administration of

diazepam as a calming agent to treat psychological shock and the replacement of fluids in the manner the attending physician finds appropriate.

This minor modification to the treatment protocol will allow attending physicians to use the limited resources they posses in the most effective manner possible. This will lead to the ultimate goal, saving as many lives as possible after a nerve agent attack.

Appendix A. Equations

Organophosphates

Slowly Perfused, Thigh, Diaphragm and Fat Tissues

$$Vt\frac{dC}{dt} = \mathrm{FtQc(Ca} - \left(\frac{\mathrm{Ct}}{\mathrm{p}}\right))$$

Brain, Liver. Kidney and Richly Perfused Tissues

$$Vt\frac{dC}{dt} = \mathrm{FtQcCa} - \left(\frac{\mathrm{FtQcCt}}{\mathrm{p}}\right) - \frac{\mathrm{VmaxCt}}{\mathrm{Km} + \mathrm{Ct}}$$

Venous Tissue

$$Vt\frac{dC}{dt} = \mathrm{Qc}\sum\mathrm{FtCt} - \mathrm{QcCv} - \left(\frac{\mathrm{FtQcCt}}{\mathrm{p}}\right) - \frac{\mathrm{VmaxCv}}{\mathrm{Km} + \mathrm{Cv}}$$

Lung Tissue

$$QpCair + QcCv = \frac{\mathrm{QpCa}}{\mathrm{p}} + \mathrm{QcCa}$$

Arterial Tissue

$$Va\frac{dC}{dt} = \mathrm{QcCl} - \mathrm{QcCa} - \frac{\mathrm{VmaxCa}}{\mathrm{Km} + \mathrm{Ca}}$$

Oxime

Brain, Diaphragm, Fat, Richly Perfused, Slowly Perfused Tissue

$$Vt\frac{dC}{dt} = \mathrm{FtQc(Ca} - \frac{\mathrm{Ct}}{\mathrm{p}})$$

Kidney Tissue

$$Vt\frac{dC}{dt} = \mathrm{FtQc(Ca} - \frac{\mathrm{Ct}}{\mathrm{p}} - \mathrm{ECa})$$

Liver Tissue

$$Vt\frac{dC}{dt} = \mathrm{FtQcCa} - \frac{\mathrm{FtQcCtCt}}{\mathrm{p}} - \frac{\mathrm{VmaxCt}}{\mathrm{Km} + \mathrm{Ct}}$$

Thigh Tissue

$$Vt\frac{dC}{dt} = \mathrm{FtQcCa} + \mathrm{IM} - \frac{\mathrm{FtQcCtCt}}{\mathrm{p}}$$

Venous Tissue

$$Vv\frac{dC}{dt} = \mathrm{Qc}\sum\mathrm{FtCt} + \mathrm{IV} - \mathrm{QcCv}$$

Arterial Tissue

$$Va\frac{dC}{dt} = \mathrm{Qc}(\mathrm{Cv} - \mathrm{Ca})$$

Atropine

Brain, Diaphragm, Fat, Richly Perfused, Slowly Perfused Tissues

$$Vt\frac{dC}{dt} = \mathrm{FtQc}(\mathrm{Ca} - \frac{\mathrm{Ct}}{\mathrm{p}})$$

Kidney Tissue

$$Vt\frac{dC}{dt} = \mathrm{FtQc}(\mathrm{Ca} - \frac{\mathrm{Ct}}{\mathrm{p}} - \mathrm{ECa})$$

Liver Tissue

$$Vt\frac{dC}{dt} = \mathrm{FtQcCa} - \frac{\mathrm{FtQcCtCt}}{\mathrm{p}} - \frac{\mathrm{VmaxCt}}{\mathrm{Km} + \mathrm{Ct}}$$

Thigh Tissue

$$Vt\frac{dC}{dt} = \mathrm{FtQcCa} + \mathrm{IM} - \frac{\mathrm{FtQcCt}}{\mathrm{p}}$$

Venous Tissue

$$Vt\frac{dC}{dt} = \mathrm{Qc}\sum\mathrm{FtCt} + \mathrm{IV} - \mathrm{QcCv}$$

Arterial Tissue

$$Va\frac{dC}{dt} = \mathrm{Qc(Cv - Ca)}$$

Acetylcholinesterase

Brain, Kidney, Diaphragm, Liver, Slowly Perfused, Richly Perfused and Thigh Tissue

$$Vt\frac{dC}{dt} = \mathrm{X1 - X2CtVt}$$

Butyrylcholinesterase

Brain, Kidney, Diaphragm, Liver, Slowly Perfused, Richly Perfused and Thigh Tissue

$$Vt\frac{dC}{dt} = \mathrm{Y1 - Y2CtVt}$$

Carboxylesterase

Brain, Kidney, Diaphragm, Liver, Slowly Perfused, Richly Perfused and Thigh Tissue

$$Vt\frac{dC}{dt} = \mathrm{Z1 - Z2CtVt}$$

Acetylcholinesterase and Organophosphate Chemical Reaction

$$\frac{d(AChE)}{dt} = Ki(AChE)(OP) - Ks\left(\frac{AChE}{OP}\right) - Ka\left(\frac{AChE}{OP}\right)$$

Butyrylcholinesterase and Oganophosphate Chemical Reaction

$$\frac{d(BuChE)}{dt} = Ki(BuChE)(OP) - Ks\left(\frac{BuChE}{OP}\right) - Ka\left(\frac{BuChE}{OP}\right)$$

Carboxylesterase and Organophasphate Chemical Reaction

$$\frac{d(CaE)}{dt} = Ki(CaE)(OP) - Ks\left(\frac{CaE}{OP}\right) - Ka\left(\frac{CaE}{OP}\right)$$

Oxime and Acetylcholinesterase-organophosphate complex chemical reaction

$$\frac{d(AChE/OP)}{dt} = Kr(\frac{AChE}{OP})(Oxime)$$

Oxime and Butyrylcholinesterase-organophosphate complex chemical reaction

$$\frac{d(BuChE/OP)}{dt} = Kr(\frac{BuChE}{OP})(Oxime)$$

Oxime and Carboxylesterase-organophosphate complex chemical reaction

$$\frac{d(CaE/OP)}{dt} = Kr(\frac{CaE}{OP})(Oxime)$$

Atropine, Acetylcholine and Acetylcholinesterase reaction

$$\frac{d(ACh\ site)}{dt} = p1\left(\frac{p1}{p1 + atropine}\right) - p2(AChE)(ACh\ site)$$

List of Symbols
Vt: Volume of tissue
dc/dt: Change in chemical concentration with respect to time
Ft: Fraction of blood flow that the tissue
Qc: Cardiac output
Ca: Chemical concentration in arterial tissue
Ct: Chemical concentration in tissue
P: Tissue to blood partition coefficient
Vmax: Maximum metabolism rate
Km: Michaelis-Menton constant
Vv: Volume of venous tissue
Cv: Chemical concentration in venous tissue
Qp: Pulmonary ventilation rate
Cair: Chemical concentration in air
Va: Volume of arterial tissue
Cl: Chemical concentration of blood in lungs
E: Elimination fraction
IM: Intramuscular injection rate
IV: Intravenous injection rate
Ki: Organophosphate reaction rate coefficient with esterase
Ks: Organophosphate-esterase complex natural separation reaction rate coefficient
Ka: Organophophate-esterase complex aging reaction rate coefficient
Kr: Organophosphate-esterase complex reaction rate coefficient with oxime
p1: Acetylcholine binding rate
p2: Acetycholine degradation constant
X1: Acetylcholinesterase synthesis rate
X2: Acetylcholinesterase degradation rate
Y1: Butyrylcholinesterase synthesis rate
Y2: Butyrylcholinesterase degradation rate
Z1: Carboxylesterase synthesis rate
Z2: Carboxylesterase degradation rate

Appendix B. Parameters

Physiological Parameters	Measurement	Source
Body Weight	60.9kg	Gearhart et al.
Cardiac Output	302 L/hr	Gearhart et al.
Pulmonary Rate	354 L/hr	Gearhart et al.
Blood Flow to Tissue Fractions		
Arterial	1	Assumed
Brain	0.134	Gearhart et al.
Diaphragm	0.006	Gearhart et al.
Richly Profused	0.2	Gearhart et al.
Fat	0.036	Gearhart et al.
Slowly Profused	0.1244	Gearhart et al.
Thigh	0.0066	Gearhart et al.
Kidney	0.223	Gearhart et al.
Liver	0.27	Gearhart et al.
Venous	1	Assumed
Tissue Volume		
Arterial	1.218 L	Gearhart et al.
Brain	1.303 L	Gearhart et al.
Diaphragm	0.183 L	Gearhart et al.
Richly Profused	2.089 L	Gearhart et al.
Fat	10.353 L	Gearhart et al.
Slowly Profused	31.899 L	Gearhart et al.
Thigh	1.681 L	Gearhart et al.
Kidney	.262 L	Gearhart et al.
Liver	2.436 L	Gearhart et al.
Venous	3.471 L	Gearhart et al.
Tissue Normalization Factors		
Arterial	.02 L/kg	Gearhart et al.
Brain	.0214 L/kg	Gearhart et al.
Diaphragm	.003L/kg	Gearhart et al.
Rapidly Profused	.0343 L/kg	Gearhart et al.
Fat	.17 L/kg	Gearhart et al.
Slowly Profused	.5238 L/kg	Gearhart et al.
Thigh	.0276 L/kg	Gearhart et al.
Kidney	.0043 L/kg	Gearhart et al.
Liver	.04 L/kg	Gearhart et al.

Venous	.057 L/kg	Gearhart et al.
Sarin Molecular Weight	140.1 mg/mmol	Gearhart et al.
Partition Coefficients		
Brain	0.67	Gearhart et al.
Diaphragm	0.77	Gearhart et al.
RPT	0.67	Gearhart et al.
Fat	17.6	Gearhart et al.
SPT	0.77	Gearhart et al.
Thigh	0.77	Gearhart et al.
Kidney	1.63	Gearhart et al.
Liver	1.53	Gearhart et al.
Arterial	1	Gearhart et al.
Venous	1	Gearhart et al.
Metabolic Parameters		
KM (Michaelis-Menton)		
Arterial	199	Gearhart et al.
Brain	440	Gearhart et al.
Kidney	134	Gearhart et al.
Liver	237	Gearhart et al.
Rapidly Profused	51	Gearhart et al.
Venous	199	Gearhart et al.
VMAX		
Arterial	5467	Gearhart et al.
Brain	470	Gearhart et al.
Kidney	5293	Gearhart et al.
Liver	70695	Gearhart et al.
Rapidly Profused	568	Gearhart et al.
Venous	16401	Gearhart et al.
Oxime Molecular Weight	132 mg/mmol	Seaman
Partition Coefficients		
Brain	0.67	Seaman
Diaphragm	0.77	Seaman
RPT	0.67	Seaman
Fat	17.6	Seaman
SPT	0.77	Seaman
Thigh	0.77	Seaman
Kidney	1.63	Seaman

Liver	1.53	Seaman
Arterial	1	Seaman
Venous	1	Seaman
Metabolic Parameters		
KM Liver	700 mg/L	Seaman
Vmax Liver	6500 mg/hr	Seaman
Kidney Partition Parameter		
Elimination Partition	0.35	Seaman
Atropine		
Molecular Weight	289 mg/mmol	Seaman
Partition Coefficients		
Brain	0.67	Seaman
Diaphragm	0.77	Seaman
RPT	0.67	Seaman
Fat	17.6	Seaman
SPT	2.1	Seaman
Thigh	2.1	Seaman
Kidney	1.63	Seaman
Liver	1.53	Seaman
Arterial	1	Seaman
Venous	1	Seaman
Metabolic Parameters		
KM Liver	700 mg/L	Gearhart
Vmax Liver	6500 mg/hr	Gearhart
Kidney Partition Parameter		
Elimination Partition	0.35	Seaman
Acetycholinesterase		
Molecular Weight	320 mg/mmol	Seaman
Synthesis Rate		
Brain	.00002 umol/hr	Gentry et al.
Diaphragm	.000003 umol/hr	Scaled from Gentry et al.
RPT	.00003 umol/hr	Scaled from Gentry et al.
Fat	0.0 umol/hr	Scaled from Gentry et al.
SPT	.0005 umol/hr	Scaled from Gentry et al.
Thigh	.00002 umol/hr	Scaled from Gentry et al.
Kidney	.000004 umol/hr	Scaled from Gentry et al.
Liver	.00004 umol/hr	Scaled from Gentry et al.
Arterial	.0001 umol/hr	Scaled from Gentry et al.

Venous	.0001 umol/hr	Gentry et al.
Initial Concentration		
Brain	.04928 umol	Gentry et al.
Diaphragm	.000909 umol	Gentry et al.
RPT	.008314 umol	Gentry et al.
Fat	0.0 umol	Gentry et al.
SPT	.222196 umol	Gentry et al.
Thigh	.011708 umol	Gentry et al.
Kidney	.000104 umol	Gentry et al.
Liver	.002424 umol	Gentry et al.
Arterial	.001212 umol	Gentry et al.
Venous	.003454 umol	Gentry et al.
Degradation Constant		
Brain	.082508251/hr	Seaman
Diaphragm	.00330033/hr	Seaman
RPT	.003603837/hr	Seaman
Fat	0	Seaman
SPT	.002250266/hr	Seaman
Thigh	.001708234/hr	Seaman
Kidney	.038461538/hr	Seaman
Liver	.01650165/hr	Seaman
Arterial	.08250825/hr	Seaman
Venous	.02895194/hr	Seaman
Butyrylcholinesterase		
Molecular Weight	83 mg/mmol	Gearhart et al.
Synthesis Rate		
Brain	.00002 umol/hr	Gentry et al.
Diaphragm	.000003 umol/hr	Scaled from Gentry et al.
RPT	.00003 umol/hr	Scaled from Gentry et al.
Fat	0.0 umol/hr	Gentry et al.
SPT	.0005 umol/hr	Scaled from Gentry et al.
Thigh	.00002 umol/hr	Scaled from Gentry et al.
Kidney	.000004 umol/hr	Scaled from Gentry et al.
Liver	.00004 umol/hr	Scaled from Gentry et al.
Arterial	.0001 umol/hr	Scaled from Gentry et al.
Venous	.0001 umol/hr	Gentry et al.
Initial Concentration		
Brain	.016859 umol	Gentry et al.
Diaphragm	.002 umol	Gentry et al.

RPT	.006236 umol	Gentry et al.
Fat	0.0 umol	Gentry et al.
SPT	.190454 umol	Gentry et al.
Thigh	.010035 umol	Gentry et al.
Kidney	.000782 umol	Gentry et al.
Liver	.019392 umol	Gentry et al.
Arterial	.00606 umol	Gentry et al.
Venous	.017271 umol	Gentry et al.
Degradation Constant		
Brain	.00118631/hr	Seaman
Diaphragm	.0015/hr	Seaman
RPT	.004810776/hr	Seaman
Fat	.004810776/hr	Seaman
SPT	.002625306/hr	Seaman
Thigh	.001993024/hr	Seaman
Kidney	.00511509/hr	Seaman
Liver	.002062706/hr	Seaman
Arterial	.01650165/hr	Seaman
Venous	.005790053/hr	Seaman
Carboxylesterase		
Molecular Weight	320 mg/mmol	Known
Synthesis Rate		
Brain	.00002 umol/hr	Gentry et al.
Diaphragm	.000003 umol/hr	Seaman
RPT	.00003 umol/hr	Seaman
Fat	0.0 umol/hr	Seaman
SPT	.0005 umol/hr	Seaman
Thigh	.00002 umol/hr	Seaman
Kidney	.000004 umol/hr	Seaman
Liver	.00004 umol/hr	Seaman
Arterial	.0001 umol/hr	Seaman
Venous	.0001 umol/hr	Gentry et al.
Initial Concentration		
Brain	.778104 umol	Gentry et al.
Diaphragm	.52722 umol	Gentry et al.
RPT	442.73754 umol	Gentry et al.
Fat	0.0 umol	Gentry et al.
SPT	73.007244 umol	Gentry et al.

Thigh	3.846888 umol	Gentry et al.
Kidney	4.29957 umol	Gentry et al.
Liver	110.292 umol	Gentry et al.
Arterial	5.0904 umol	Gentry et al.
Venous	14.50764 umol	Gentry et al.
Degradation Constant		
Brain	2.57035*10-5/hr	Seaman
Diaphragm	5.69022*10-6/hr	Seaman
RPT	6.77602*10-8/hr	Seaman
Fat	0	Seaman
SPT	6.848864*10-6/hr	Seaman
Thigh	5.19901*10-6/hr	Seaman
Kidney	9.30326*10-7/hr	Seaman
Liver	3.626674*10-7/hr	Seaman
Arterial	1.96448*10-5/hr	Seaman
Venous	6.89292*10-6/hr	Seaman
Acetycholine		
Molecular Weight	146 mg/mmol	Holder
Activation Rate Constants		
Brain	.00719488 mg/hr	Holder
Diaphragm	.000132714 mg/hr	Holder
RPT	.001213844 mg/hr	Holder
SPT	.032440616 mg/hr	Holder
Thigh	.001709368 mg/hr	Holder
Kidney	.000015184 mg/hr	Holder
Liver	.000353904 mg/hr	Holder
Reaction Rate Coefficients		
AChE		
Ka	0.1386/hr	Assumed
Ki	220000 /mmol(hr)	Assumed
Kr	100/mmol(hr)	Assumed
Ks	1/hr	Assumed
BuChE		
Ka	.054/hr	Assumed
Ki	110000	Assumed
Kr	300/hr	Assumed
Ks	1/hr	Assumed
CaE		

Ka	0	Assumed
Ki	110000/hr	Assumed
Kr	300/hr	Assumed
Ks	1/hr	Assumed
K AcH-AcHE	20292.23826/hr	Assumed

Appendix C. Test Results

Model Verification Mild Symptoms

TEST #	Ct(concentration*time)	Exposure Time (Minutes)	ATROPINE DOSE/Time	OXIME DOSE/Time	Symptom Level Max.	Rebound Symptom Max.	Recovery
1	.75=(.15*5)	5	2mg/15 min	600mg/15min	1	0	yes
2	1.5=(.15*10)	10	2mg/15 min	600mg/15min	1.14	0	yes
3	1.5=(.1*15)	15	2mg/15 min	600mg/15min	1.15	0	yes
4	.75=(.15*5)	5	2mg/20 min	600mg/20 min	1.03	0	yes
5	1.5=(.15*10)	10	2mg/20 min	600mg/20 min	1.15	0	yes
6	1.5=(.1*15)	15	2mg/20 min	600mg/20 min	1.2	0	yes
7	.75=(.15*5)	5	2mg/30 min	600mg/30 min	1.04	0	yes
8	1.5=(.15*10)	10	2mg/30 min	600mg/30 min	1.19	0	yes
9	1.5=(.1*15)	15	2mg/30 min	600mg/30 min	1.25	0	yes

Model Verification Incapacitating Symptoms

TEST #	Ct(concentration*time)	Exposure Time (Minutes)	ATROPINE DOSE/Time	OXIME DOSE/Time	Symptom Level Max.	Rebound Symptom Max.	Recovery
10	2.0=(.4*5)	5	6mg/15 min	1800mg/15min	1.34	0	yes
11	3.0=(.3*10)	10	6mg/15 min	1800mg/15min	1.41	0	yes
12	2.25=(.15*15)	15	6mg/15 min	1800mg/15min	1.48	0	yes
13	1.75=(.35*5)	5	6mg/20 min	1800mg/20 min	1.62	0	yes
14	2.0=(.2*10)	10	6mg/20 min	1800mg/20 min	1.69	0	yes
15	2.25=(.15*15)	15	6mg/20 min	1800mg/20 min	1.75	0	yes
16	1.75=(.35*5)	5	6mg/30 min	1800mg/30 min	1.62	0	yes
17	2.0=(.2*10)	10	6mg/30 min	1800mg/30 min	1.89	0	yes
18	2.25=(.15*15)	15	6mg/30 min	1800mg/30 min	1.94	0	no

Test for Re-Bound in Symptoms

TEST #	Ct(concentration*time)	ExposureTime (Minutes)	OXIME DOSE/Time	Symptom Level Max.	Recovery Symptom Level Min.	Rebound Symptom Max.	Rebound Max-Recovery Min	Method of Oxime Infusion
19	1.5=(.15*10)	10	600mg/30min	1.38	1.21	1.2	0.01	IM
20	1.5=(.15*10)	10	600mg/45min	1.38	1.09	1.1	0.01	IM
21	1.5=(.15*10)	10	600mg/60min	1.38	1.06	1.07	0.01	IM
22	1.5=(.15*10)	10	600mg/30min	1.38	1.21	1.26	0.5	IV
23	1.5=(.15*10)	10	600mg/45min	1.38	1.09	1.12	0.3	IV
24	1.5=(.15*10)	10	600mg/60min	1.38	1.06	n/a	n/a	IV
25	1.5=(.15*10)	10	200mg/30min	1.38	1.21	1.26	0.5	IV
26	1.5=(.15*10)	10	200mg/45min	1.38	1.1	1.14	0.3	IV
27	1.5=(.15*10)	10	200mg/60min	1.38	1.06	n/a	n/a	IV

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14. ABSTRACT
The 2010 National Security Strategy states, "The effective dissemination of a lethal agent would endanger the lives of thousands of people and have unprecedented economic, societal, and political consequences. We must continue to work at home with first responders and health officials to reduce the risk associated with high-consequence threats". Nerve agents, such as Sarin gas, are considered high consequence threats. The threat of use of agents such as Sarin is as much a threat today as any other time in our history. However, the suggested treatment protocol for someone is not as precise as it could be. Debate exists over the dosing and timing of atropine and oxime treatment when combating the effects caused by exposure to nerve agents. Oxime treatment has proved to be less than effective under several situations. The research presented in this paper used a physiologically based pharmacokinetic model to determine if the current treatment protocol prescribed by the Center for Disease Control (CDC) and the U.S Army is effective in treating victims suffering from acute exposure symptoms. The model was used to determine what treatment should be applied to victims suffering from mild exposure symptoms. The results indicate that the current treatment prescribed by the CDC and U.S. Army is effective; however treatment with oxime therapy was not effective in alleviating symptoms for someone suffering from mild exposure. By applying these results a treatment protocol was developed for someone suffering from mild exposure symptoms to Sarin gas.

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